DOCUMENT RESUME

ED 466 915 EC 309 063

TITLE	Autism: Present Challenges, Future Needs--Why the Increased Rates? Hearing before the Committee on Government Reform. House of Representatives, One Hundred Sixth Congress, Second Session (April 6, 2000).
INSTITUTION	Congress of the U.S., Washington, DC. House Committee on Government Reform.
REPORT NO	House-Hrg-106-180
PUB DATE	2001-00-00
NOTE	483p.
AVAILABLE FROM	Government Printing Office, Superintendent of Documents, Congressional Sales Office, Washington, DC 20402-9328. Tel: 202-512-1800. For full text: http://www.house.gov/reform.
PUB TYPE	Legal/Legislative/Regulatory Materials (090)
EDRS PRICE	EDRS Price MF02/PC20 Plus Postage.
DESCRIPTORS	*Autism; *Child Health; Children; *Disease Control; *Etiology; Family Problems; Hearings; *Immunization Programs; Incidence; Influences; Parent Attitudes; *Preventive Medicine; Research Needs; Symptoms (Individual Disorders)
IDENTIFIERS	Congress 106th; Vaccination

ABSTRACT

This document contains the proceedings of a hearing on April 6, 2000, before the U.S. House of Representatives Committee on Government Reform. The hearing addressed the increasing rate of children diagnosed with autism, possible links between autism and childhood vaccinations, and future needs of these children. After opening statements by congressmen on the Committee, the statements and testimony of Kenneth Curtis, James Smythe, Shelley Reynolds, Jeana Smith, Scott Bono, and Dr. Wayne M. Danker, all parents of children with autism, are included. Their statements discuss symptoms of autism, vaccination concerns, family problems, financial concerns, and how parents can be helped. The statements and testimony of the second panel are then provided, including that of Andrew Wakefield, John O'Leary, Vijendra K. Singh, Coleen A. Boyle, Ben Schwartz, Paul A. Offit, and Brent Taylor. These doctors and disease control experts discuss the possible relationship between vaccinations and autism. Following, the statement and testimony of Walter O. Spitzer discusses the epidemiology of autism and childhood vaccinations. The statements and testimony of the next panel are then provided, including that of Bernard Rimland, Michael J. Goldberg, Mary N. Megson, John E. Upledger, Cathy L. Pratt, Deborah G. Hirtz, and Edwin H. Cook. These doctors discuss the safety of vaccinations, research needs in the autism field, and possible causes of autism. (CR)

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AUTISM: PRESENT CHALLENGES, FUTURE NEEDS—WHY THE INCREASED RATES?

HEARING

BEFORE THE

COMMITTEE ON GOVERNMENT REFORM

HOUSE OF REPRESENTATIVES

ONE HUNDRED SIXTH CONGRESS

SECOND SESSION

APRIL 6, 2000

Serial No. 106–180

Printed for the use of the Committee on Government Reform

Available via the World Wide Web: http://www.gpo.gov/congress/house
http://www.house.gov/reform

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69–622 DTP WASHINGTON : 2001

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CONTENTS

Page

Hearing held on April 6, 2000 1

Statement of:

- Curtis, Kenneth, Catonsville, MD; James Smythe, Carmel, IN; Shelley Reynolds, Baton Rouge, LA; Jeana Smith, Denham Springs, LA; Scott Bono, Durham, NC; and Dr. Wayne M. Dankner, San Diego, CA 49
- Rimland, Bernard, Ph.D., Autism Research Institute, San Diego, CA; Dr. Michael J. Goldberg, Director, NIDS Medical Advisory Board, Tarzana, CA; Dr. Mary N. Megson, Pediatric and Adolescent Abilities Center, Richmond, VA; Dr. John E. Upledger, the Upledger Institute, Clearwater, FL; Cathy L. Pratt, Indiana Resource Center for Autism; Dr. Deborah G. Hirtz, National Institutes of Health; Dr. Edwin H. Cook, Jr., University of Chicago 327
- Spitzer, Dr. Walter O., professor emeritus of epidemiology, McGill University, and member, National Academy of Science of the United States, Corpus Christi, TX 187
- Wakefield, Dr. Andrew, Royal Free and University College Medical School, London, England; Dr. John O'Leary, Coombe Women's Hospital, Dublin, Ireland; Vijendra K. Singh, Utah State University; Coleen A. Boyle, Centers for Disease Control and Prevention, U.S. Department of Health and Human Services, accompanied by Dr. Ben Schwartz, Acting Director, Epidemiology and Surveillance Division, CDC; Dr. Paul A. Offit, University of Pennsylvania School of Medicine; and Dr. Brent Taylor, Royal Free and University College Medical School, London, England 101

Letters, statements, et cetera, submitted for the record by:

- Bono, Scott, Durham, NC, prepared statement of 85
- Boyle, Coleen A., Centers for Disease Control and Prevention, U.S. Department of Health and Human Services:
  - Prevalence of Autism report 198
  - Prepared statement of 148
- Cook, Dr. Edwin H., Jr., University of Chicago, prepared statement of 463
- Curtis, Kenneth, Catonsville, MD, prepared statement of 52
- Dankner, Dr. Wayne M., San Diego, CA, prepared statement of 90
- Goldberg, Dr. Michael J., Director, NIDS Medical Advisory Board, Tarzana, CA, prepared statement of 339
- Hirtz, Dr. Deborah G., National Institutes of Health, prepared statement of 450
- Megson, Dr. Mary N., Pediatric and Adolescent Abilities Center, Richmond, VA, prepared statement of 424
- O'Leary, Dr. John, Coombe Women's Hospital, Dublin, Ireland, prepared statement of 128
- Offit, Dr. Paul A., University of Pennsylvania School of Medicine, prepared statement of 165
- Pratt, Cathy L., Indiana Resource Center for Autism, prepared statement of 444
- Reynolds, Shelley, Baton Rouge, LA, prepared statement of 70
- Rimland, Bernard, Ph.D., Autism Research Institute, San Diego, CA, prepared statement of 331
- Singh, Vijendra K., Utah State University, prepared statement of 142
- Smith, Jeana, Denham Springs, LA, prepared statement of 77
- Smythe, James, Carmel, IN, prepared statement of 58
- Taylor, Dr. Brent, Royal Free and University College Medical School, London, England, prepared statement of 173

Page

Letters, statements, et cetera, submitted for the record by—Continued
  Upledger, Dr. John E., the Upledger Institute, Clearwater, FL, prepared statement of 435
  Wakefield, Dr. Andrew, Royal Free and University College Medical School, London, England, prepared statement of 107
  Waxman, Hon. Henry A., a Representative in Congress from the State of California:
    Documents from the Autism Autoimmunity Project 230
    Various prepared statements 8

AUTISM: PRESENT CHALLENGES, FUTURE NEEDS—WHY THE INCREASED RATES?

THURSDAY, APRIL 6, 2000

House of Representatives,
Committee on Government Reform,
Washington, DC.

The committee met, pursuant to notice, at 10:37 a.m., in room 2154, Rayburn House Office Building, Hon. Dan Burton (chairman of the committee) presiding.

Present: Representatives Burton, Morella, Ros-Lehtinen, McHugh, Horn, LaTourette, Hutchinson, Terry, Biggert, Ose, Chenoweth-Hage, Waxman, Norton, Kucinich, Tierney, and Turner.

Staff present: Kevin Binger, staff director; Daniel R. Moll, deputy staff director; David A. Kass, deputy counsel and parliamentarian; Mark Corallo, director of communications; S. Elizabeth Clay, Nicole Petrosino, and Nat Weinecke, professional staff members; Robert Briggs, deputy chief clerk; Robin Butler, office manager; Michael Canty, legislative aide; Scott Fagan and John Sare staff assistants; Toni Lightle, legislative assistant; Leneale Scott, computer systems manager; Lisa Smith Arafune, chief clerk; Corinne Zaccagnini, systems administrator; Phil Schiliro, minority staff director; Sarah Despres, minority counsel; Ellen Rayner, minority chief clerk; Teresa Coufal, minority staff assistant; Jean Gosa and Earley Green, minority assistant clerks; and Andrew Su, minority research assistant.

Mr. Burton. If I could have your attention, please. I know a lot of people have cameras, and I hate to throw a wet blanket on those of you who want to take some pictures, but unless you are a member of the media, I wish you would not take any pictures during the hearing. We will try to get the people you want to take pictures of together later; but please do not take a bunch of pictures during the meeting because it will probably disrupt what we are trying to accomplish.

Good morning. A quorum being present, the Committee on Government Reform will come to order.

I ask unanimous consent that all Members' and witnesses opening statements be included in the record. Without objection, so ordered.

I also ask unanimous consent that all articles, exhibits, and extraneous or tabular material referred to be included in the record. Without objection, so ordered.

We do have some Members who have opening statements, and we will allow those, and if they do not choose to give an opening statement and want to prepare one for the record, that will be fine as well.

This morning we are here to talk about autism. As we learned in our August hearing, the rates of autism have escalated dramatically in the last few years. What used to be considered a rare disorder has become a near epidemic. We have received hundreds of letters from parents across the country. In fact, here are some notebooks, and each one of the pages represents a parent who has a problem with a child with autism.

They have shared with us their pain and their challenges. My staff tells me that some of them cried when they read some of these letters—and I have a pretty hard-nosed staff.

I do not have to read a letter to experience the kind of heartbreak that is in these letters. I see it in my own family. I am very proud of this picture. The one on the left is my grand-daughter, who almost died after receiving a hepatitis B shot. Within a short period of time, she quit breathing, and they had to rush her to the hospital.

My grandson, Christian, whom you see there with his head on her shoulder, according to the doctors was going to be about 6-foot-10—we anticipated having him support the family by being an NBA star—but unfortunately, after receiving nine shots in 1 day, the MMR and the DTaP shot and the hepatitis B, within a very short period of time, he quit speaking, ran around banging his head against the wall, screaming, hollering, waving his hands, and became a totally different child. We found out that he was autistic.

He was born healthy. He was beautiful and tall. He was outgoing and talkative. He enjoyed company and going places. Then, he had those shots, and our lives and his life changed.

I do not want to read all the things that happened to Christian, because I am not sure I could get through it. But unfortunately, what happened to Christian is not a rare, isolated event. Shelley Reynolds will testify today. Her organization, Unlocking Autism, will be displaying thousands of pictures of autistic children at the "Hear Their Silence" autism rally this Saturday.

Forty-seven percent of the parents who provided these pictures feel that their children's autism is linked to the immunizations—almost half. We frequently hear about the children with chronic ear infections and children who became autistic after spiking a fever with their vaccinations. Liz Birt was one of the hundreds of parents who contacted us. Her 5-year-old son Matthew has been classified as autistic. He was developing normally. At age 15 months, following his MMR vaccine, he began to regress. Since the time of his vaccination, he has had chronic diarrhea. This is his picture—a good-looking kid.

This is very prevalent, this chronic diarrhea, in autistic children. Matthew also did not sleep on a regular basis for over 3 years. Liz took her son to numerous gastroenterologists in prominent medical facilities in the United States with no resolution. Finally, this past November, Liz took her son to London, to the Royal Free Hospital. A team of medical experts there examined Matthew. They felt that he had a bowel obstruction. To the family, this seemed impossible since he had constant diarrhea. An x-ray indicated that Matthew had a fecal mass in his colon the size of a cantaloupe. After the obstruction was cleared with laxatives, Matthew underwent an endoscopy and colonoscopy. The lesions in Matthew's bowel tested positive for the measles virus.

Dr. Andrew Wakefield and Professor John O'Leary will be testifying today. Their research has uncovered a possible connection between inflammatory bowel disorder in children with autism who receive the MMR vaccine and have measles virus in their small intestines.

Since coming home from England and being treated for chronic inflammatory bowel disorder, Matthew has finally begun to sleep through the night. I know that is a welcome relief for his family.

Unfortunately, Matthew's story is not that unusual in children with autism. Our grandson has a similar problem. Unfortunately, it is important that I make two things very clear today. I, and I believe every Member of Congress, am not against vaccinations, and I do not think that every autistic child acquires autism after receiving childhood immunizations.

I think slide 3 shows a lot of children who have had autism—is that correct—those are before-and-after pictures of the children.

However, there is enough evidence emerging of some kind of connection for some children that we cannot close our eyes to it—we have to learn more.

Dr. Mary Megson of Richmond, VA will testify about the correlation she has seen in children with autism and attention deficit disorder. She has seen a correlation between Vitamin A depletion and immune suppression after receiving the MMR vaccination.

There are certainly children who are born with autism. They have what can be called "classical autism." There is, however, a growing number of children who are growing normally and then acquire autism, or "atypical autism."

There most probably is a genetic component to autism, but genetics is not the only issue. Many children seem to have severe food sensitivities, particularly to gluten and casein, ingredients in the most common foods, dairy and wheat. Many of these children show signs of autism shortly after receiving their immunizations. Some of these children, as we will hear from Jeana Smith, have metal toxicities, aluminum and mercury. What is the source of these toxic substances?

Dr. Goldberg will testify that maybe what we are seeing is not autism at all, but a neuro-immunologic dysfunction.

I am very concerned about the increased number of childhood vaccines. I am concerned about the ingredients that are put in these vaccines. I am concerned about the way they are given. We have learned that most of the vaccines our children are given contain mercury, aluminum and formaldehyde. Last year, the FDA added up the amount of mercury our babies are being given to learn that in the first 6 months of life, they receive more mercury than is considered safe. Think about that—in the first 6 months of life, the FDA has said that children are receiving more mercury than is considered safe, and most of that is from vaccinations. Why is it that the FDA licenses vaccines that contain neurotoxins like mercury and aluminum?

When asked about the increased rates of autism, many will immediately discount that there is even an increase—even though the latest statistics from the Department of Education show increased rate in every, single State. This slide shows you that every State has seen a dramatic increase.

Others will say the increase is due to better diagnostic skills. Others will say it is because the diagnostic category was expanded. If we look at the slide showing California here, California has reported a 273 percent increase in children with autism since 1988. From this increase, 21 percent of all autistic children in California live in the 29th District, which is Henry Waxman's district, who is the ranking Democrat on our committee.

Florida has reported a 571 percent increase in autism. Maryland has reported a 513 percent increase between 1993 and 1998. You cannot attribute all of that to better diagnostic skills.

In 1999, there are 2,462 children ages 3 to 21 in Indiana diagnosed with autism. That is one-fourth of 1 percent of all the school children in Indiana, or 1 out of every 400; 23 percent of these children live in my district, the 6th District of Indiana.

This increase is not just better counting. If we want to find a cure, we must first look to the cause. We must do this now, before our health and education systems are bankrupted, and before more of our Nation's children are locked inside themselves with this disease.

Kenneth Curtis, part of "Dave's Morning Show" at Oldies 100 FM here in Washington, will set the stage by talking about being the parent of an autistic child. He will be followed by James Smythe, of Carmel, IN. He will share how, through properly looking at autism as an illness and addressing that illness, his son is improving.

Scott Bono, from North Carolina, lives close to one of the finest medical facilities in the world—Duke University. However, he has been unable to find medical experts to properly address his autistic son's needs. He is forced to drive 12 hours every 4 weeks for his son's medical treatments.

Dr. William Dankner, the father of a 13-year-old daughter with autism, and a scientist, will testify about the challenges of finding therapies and treatments that have adequate research. He will also talk about the battle of getting adequate education through the public school system. I think all of us who have autistic children or grandchildren know the problems that it involves.

We hear repeatedly that parents are not informed at the time of diagnosis by their school system what educational options an autistic child is entitled to. It is only after hiring lawyers and going through the legal process that many children have access to appropriate educational opportunities. We are learning that the earlier autism is diagnosed and treatments are begun, the better it is for the child. Indiana is fortunate to have the First Steps Early Intervention System, a nationally recognized system that provides early intervention services for children up to 2 years of age.

Families are forced to spend huge sums of money out-of-pocket even when they have good insurance, because autism is often specifically excluded. We need to talk to State legislators around this country to tell them how important it is, with the explosion of autism, that these benefits be mandated by the States and be covered by insurance.

California passed legislation recently to require insurance companies to cover autism. Parents spend $20,000 to $30,000 a year. What medical care is covered is often done after extensive struggles with insurance companies.

We have a long hearing scheduled today with a broad spectrum of ideas presented. We will have a variety of medical approaches presented. We will hear about secretin, which gained a great deal of media attention in the past year and from which many parents have seen tremendous success.

Dr. John Upledger, a former adviser to the Office of Alternative Medicine at the National Institutes of Health, will testify on the use of craniosacral therapy. He is the director of the Upledger Institute in Palm Beach Gardens, FL. For more than 25 years, Dr. Upledger has been treating autistic children and helping families through this approach. Craniosacral therapy is a gentle, powerful form of body work that directly influences the brain and spinal cord. It is used to treat pain, discomfort, or trauma to the head or face, including TMJ dysfunction and headaches. Craniosacral therapy can also relieve physical and emotional trauma.

In addition to his work with autism, Dr. Upledger has achieved dramatic results in treating post-traumatic stress disorder in Vietnam veterans.

In addition to medical treatments for the physical symptoms of autism, there are numerous therapies that are needed to help autistic children. Special educational approaches are needed that can include intensive behavior modification, known as ABA, Lovass, music therapy, speech therapy, auditory integration and sensory integration, as well as play therapy.

We will hear from both the Centers for Disease Control and Prevention and the National Institutes of Health about ongoing research and future needs. Of particular interest is the Brick Township study which has been evaluating a cluster of autism in New Jersey.

This hearing will raise more questions than we can answer today. We owe it to our children and to our grandchildren to ensure that we are being diligent in looking for the causes of autism. We have to do everything humanly possible to determine if there is something that can be done to unlock our children from the prison that they are in as a result of autism. I think that as a top priority, we have to do much more research on the potential connection between vaccines and autism. We cannot stick our heads in the sand and ignore this possibility.

If we do not take action now, 10 years from now, it may be too late, not only for this generation of children, but for our taxpayer-funded health and education systems, which could collapse from trying to care for all of these children.

The hearing record will remain open for 2 weeks.

I now yield to my colleague from California, Mr. Waxman, for his opening statement.

Mr. WAXMAN. Thank you very much, Mr. Chairman.

I am glad we are having this hearing today on autism. We still have many questions about autism—what causes it; what are the safest and most effective treatments; is there a way to prevent it; how many people in the country suffer from autism?

We do know some things about autism. We know there is a genetic component to autism. There have been some dramatic discoveries recently in the genetics of autism like the discovery of the Fragile X gene and the gene that causes Rett syndrome. We know that autism most likely develops very early during fetal development. We also know that parents are not to blame for autism. We have come a long way from the time when fathers and mothers were led to believe that they had done something to cause their children's autism, leaving them with needless and destructive guilt.

But I also understand that this hearing was called to consider a theory that certain vaccines cause autism. From my discussions with medical experts, scientists, and the autism community, it is clear that this is only a theory. As the American Medical Association concluded recently, "Scientific data does not support a causal association between vaccination and autism."

I believe that we need to increase our efforts to understand the causes of autism. In this search, no possible cause, including vaccines, should be off the table. That is why I am a cosponsor of H.R. 3301, which would provide additional funding at NIH for research into what causes autism, how many people suffer from autism, and how best to treat those who have autism.

But in this process, we must not get ahead of the science or raise false alarms. At every hearing in this Congress that this committee has held touching on childhood immunizations, I have made a point of emphasizing the tremendous public health value of immunization. More Americans have been saved by vaccines than by any other medical intervention. Across the globe, 2.5 million children die every year from childhood diseases; another 750,000 are crippled by these diseases. But American children are shielded from this death and misery by their vaccinations.

During my 25-year career in Congress, my focus has been on improving health care, especially for children. When I was chairman of the Health and Environment Subcommittee of the Commerce Committee from 1979 to 1994, we worked constantly to expand NIH research into childhood diseases. I have continued to fight for more research, better treatments, and coverage while I have been in the minority. During countless hearings and many legislative battles, I have heard over and over again about the pain of parents whose children suffer from debilitating diseases.

So I sympathize with the parents who are here today. I know how painful and how hard it must be for you as parents to have children who appear to be developing normally and then, all of a sudden, seemingly out of nowhere, stop communicating and stop developing.

We need to do everything we can to give these parents here and other parents around the country answers. There is still much to learn. In medicine the best answers come from research that can withstand the rigors of the scientific method. These standards have been developed in order to find the truth. If research has been conducted with control groups, and the results have been independently validated, then that gives parents meaningful information about what causes a disease or a condition and what the best treatments are.

Parents and doctors need the best possible information so that they can make the best possible decisions regarding their children's health.

There are lots of experts and groups that are knowledgeable about this issue but who were not invited to testify today. These groups include Dr. Louis Sullivan, former Secretary of Health and Human Services, and current president of the Morehouse School of Medicine; Dr. Isabelle Rapin, from the Albert Einstein College of Medicine; the American Public Health Association; the American Medical Association, and the National Network for Immunization Information. At this time I would ask unanimous consent that all of their statements be entered into the record.

Mr. BURTON. Without objection, so ordered.

[The information referred to follows:]

JAMES C. GREENWOOD
8TH DISTRICT, PENNSYLVANIA

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Statement of Congressman James C. Greenwood
to the House Committee on Government Reform
April 6, 2000

Chairman Burton, I appreciate the lead you have taken on behalf of the parents and victims of Autism, and for holding this hearing today. Autism truly is a silent epidemic. Your commitment to understanding the origins of autism are laudable and directly point to a need for a greater federal commitment to epidemiological and basic clinical research to get to the root cause of this devastating developmental disorder.

Because we don't know what causes Autism, Congressman Chris Smith and myself have spearheaded legislative efforts to improve surveillance of the disease and enhance federal research to prevent, treat and one day cure this developmental disorder.

Autism is a severe, lifelong neurological disorder that usually manifests in children during the first two years of life and causes severe impairment in language, cognition and communication. For over forty years autism was thought to be an emotional disorder caused by trauma or bad parenting. This tragic mistake resulted in the loss of an entire generation of children to medical progress. Now that we know that autism is, in fact, a medical disorder for which medical treatments and a cure can and will be found, we must devote appropriate resources.

It is the third most common developmental disorder to affect children, following mental retardation and cerebral palsy. Autism currently affects over 400,000 individuals in the U.S. and 1 in every 500 children born today. Autism is more prevalent than Down syndrome, childhood cancer or cystic fibrosis.

Some evidence links the disorder to environmental factors, as evidenced by autism "clusters" located in and around Chris Smith's district. Others point to genetic causes, and still some point to a combination of the two. Finally, some believe passionately that vaccines cause autism. The bottom line is that we just don't know. It might be vaccinations, but it might not.

The good news is that vaccines, one of the greatest medical accomplishments ever achieved, are available and are the best line of defense against many infectious diseases.

Due to the use of vaccines, smallpox has been eliminated, polio is nearly wiped out and, if immunization rates remain high, the eradication of the measles, pertussis and rubella are close. Millions of lives have been saved through vaccination and countless children have been sparred the pain and suffering of diseases like diphtheria, smallpox and polio that plagued our nation only a generation ago.

Leading health organizations including the Centers for Disease Control and Prevention (CDC), World Health Organization (WHO), American Medical Association (AMA), American Academy of Pediatrics (AAP) and American Academy of Family Physicians (AAFP) recommend routine immunization against numerous vaccine preventable diseases.

Advances in medicine have given us the gift to forget the devastating effects of diseases, including polio and small pox. Yet diseases just as ruinous and easily preventable are very real for millions of people today throughout the world. Scientific evidence indicates that side effects associated with vaccination are extremely rare and we cannot assume that adverse events associated with vaccination are necessarily caused by the vaccine. Furthermore, there has been no data or scientific proof to link vaccines to serious adverse events, including autism.

That is why we need to consider and quickly pass H.R. 3301, the Children's Health Research and Prevention Amendments, currently before the Commerce Committee. Briefly, the bill will expand research and prevention activities in a number of childhood diseases, but with specific respect to autism, the legislation will:

- Create up to five Centers of Excellence for autism. These university sites would combine clinical and basic research in autism, draw the attention of the nation's top scientists, and exist as part of a network that enables findings to be rapidly disseminated and replicated. This exact approach has been very effective in Alzheimer's and childhood leukemia.

- Create a centralized and open facility for gene and brain banking. These are essential for scientific progress in autism.

- Develop an awareness campaign for the public and physicians. Greater awareness means earlier diagnosis that can lead to better outcomes and more independent people. Currently, some physicians often do not understand autism or know how to diagnose it, thus losing valuable months, and sometimes years, of potentially critical treatment.

- Bring together the resources of the National Institutes of Health (NIH), the Centers for Disease Control (CDC) and the Department of Health and Human Services (DHHS) to attack the problem of autism.

We need to pass this bill to begin to unravel the mystery of autism. Parents and their children expect nothing less. Once again, Chairman Burton, thank you for raising this issue and for all your work on behalf of parents and children.

Statements from Health Care Professionals and Medical Associations

- "Scientific evidence does not support a causal association between vaccination and autism."

  "The theoretical causes of autism rule out vaccination as a causal factor."
  -American Medical Association

- "The best available science indicated that the development of autism is completely unrelated to use of the MMR or any other vaccine...In fact, the best evidence demonstrates that autism results from complex genetic factors and therefore originates prior to birth, not afterward."
  -Louis W. Sullivan, M.D., former Secretary of Health and Human Services

- "The lack of data to support a connection between vaccine and autism makes sense given the increasing body of information concerning when the neurobiological differences associated with autism first occur. The preponderance of evidence tells us that autism happens to our children before birth, not after."
  -The National Alliance for Autism Research (NAAR)

- "Allegations that vaccination causes autism represent unsubstantiated claims which have not been supported by credible science. Yes, there is need for continuing research on causes, prevention and treatment of autism. In the meantime, it would be tragic if parents avoid fully immunizing their children for fear of causing autism."
  -Isabelle Rapin, M.D. Professor, Neurology and Pediatrics,
  Albert Einstein College of Medicine

- "Our conclusion, based on the findings of our study, is that there is no evidence of a causal association between MMR vaccine and autism."

  "In our study we showed that the increase in the prevalence of diagnosed autism in recent birth cohorts occurred during a time when the coverage of MMR vaccine in the same cohorts has been constant. The rise cannot therefore be related to the use of MMR vaccine."
  -Dr. Elizabeth Miller and Dr. Paddy Farrington (from "Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association," *Lancet* (1999; 353:2026-20).

- "While PKIDs advocates for additional resources for autism research, it does not condone the spread of false and misleading information linking autism to childhood vaccination. PKIDs strongly encourages parents to continue immunizing their children with scientifically proven safe and effective vaccines."
  -Parents of Kids with Infections Diseases (PKIDs)

- "We also feel it is our obligation to make clear that the current scientific evidence shows that autism is not related to immunizations."
  -National Network for Immunization Information

National Coalition for Adult Immunization

4733 Bethesda Avenue · Suite 750 · Bethesda, MD 20814-5228
(301) 656-0003 · Fax: (301) 907-0878 · E-mail: adultimm@aol.com

March 31, 2000

The Honorable Daniel Burton
Chairman, Committee on Government Reform
United States House of Representatives
2157 Rayburn House Office Building
Washington, DC 20515

Dear Representative Burton:

The National Coalition for Adult Immunization (NCAI) is deeply concerned that the congressional hearings on vaccine safety may exacerbate false perceptions of risks associated with vaccines.

We recognize the importance of utilizing immunizations to protect Americans of all ages against vaccine-preventable diseases. The viruses and bacteria that cause these diseases continue to exist and cause significant rates of illness and death. The incidence of infection with these agents has drastically reduced, and this reduction is attributable to the development and utilization of vaccines.

We appreciate the potential risks involved with the practice of vaccination, but feel that the benefits achieved from the appropriate utilization of safe vaccines far outweighs these risks and the greater risks of withholding vaccinations. Unsubstantiated claims about vaccine safety, including the perceived link to autism, could result in many Americans choosing to decline vaccinations for themselves and their children. Such actions would be detrimental to the progress made in protecting the public health from debilitating and sometimes fatal vaccine-preventable diseases such as measles, rubella, polio, and mumps.

NCAI believes that the practice of immunization has had and will continue to have profound and positive impacts on public health. Initiatives to increase the rate of childhood and adult immunizations have been quite successful, but opportunities to further improve immunization rates still exist. These opportunities for improvement exist mostly because of misconceptions about vaccination and discrepancies in access to vaccinations. The NCAI is committed to further reducing the incidence of vaccine-preventable diseases by raising the awareness of Americans regarding these diseases and their prevention through the appropriate use of safe and effective vaccines, by supporting research into new protective measures, and by supporting further research to ensure the safety of vaccines.

Sincerely,

Peggy S. Webster

Peggy S. Webster, M.D., F.A.A.P.
Director

cc: Representative Waxman

Shots by age two if they're important to you.

Every Child By Two

The Carter/Bumpers Campaign For Early Immunization

The Honorable Henry Waxman
Ranking Member
House Committee on Government Reform
B-350A Rayburn House Office Building
Washington, DC 20515

RE: Vaccine Safety Hearings

Every Child By Two (ECBT) is deeply concerned that the congressional hearings on vaccine safety, led by Indiana Congressman Dan Burton, are creating a false perception of the risks associated with vaccines.

While no vaccine is 100 percent safe, unsubstantiated claims about vaccine safety, including its perceived link to autism, could result in children not being vaccinated. Such actions will only hurt our children by increasing their risk of developing debilitating and sometimes fatal vaccine-preventable diseases, such as whooping cough, measles and meningitis, among others.

ECBT supports the continued use of federal funds to determine the cause or causes of autism and increased research to improve the safety of all vaccines -- those on the market and in development -- to ensure that our children are being given the safest and most effective vaccines available. We also support efforts to strengthen the U.S. Food and Drug Administration's drug surveillance systems to track adverse events that may be caused by vaccines.

The widespread use of childhood immunizations to prevent disease has been one of the most successful public health achievements of the last 100 years, saving millions of lives. At a time when childhood immunizations are at an all-time high, exaggerating the perceived risks of vaccines will only weaken our country's successful immunization program at the expense of our children.

Sincerely,

Amy Pisani

Amy Pisani
Executive Director

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IEAC
healthy mothers, healthy babies
IMMUNIZATION EDUCATION AND ACTION COMMITTEE

Statement of the Immunization Education and Action Committee (IEAC) of the National Healthy Mothers, Healthy Babies Coalition

Steering Committee Members

Jack Blane
Chair
Rotary International

Thomas Tonniges, MD
Vice Chair
American Academy of Pediatrics

Anita Boles
National Healthy Mothers, Healthy Babies Coalition

Virginia Burggraf
American Nurses Foundation

Magdalena Castro-Lewis
National Coalition of Hispanic Health and Human Services Organizations

L. H. "Dig" DeGarmo
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Bernadette Freeland-Hyde
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aire Hannan
Association of State and Territorial Health Officials

Kathy McNamara
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Martin Smith, MD
American Academy of Pediatrics

Mark S. Smolinski, MD
Office of the Surgeon General & Assistant Secretary for Health

Cassandra Sparrow
Congress of National Black Churches

Mary Thorngren
National Coalition of Hispanic Health and Human Services Organizations

Patricia Tompkins
National Black Nurses Association

William C. Watson
All Kids Count

IEAC Program Manager
Dena Wichansky
National Healthy Mothers, Healthy Babies Coalition

The Immunization Education and Action Committee (IEAC) of the National Healthy Mothers, Healthy Babies Coalition (HMHB) is deeply concerned that the congressional hearings on vaccine safety, led by Indiana Congressman Dan Burton, are creating a false perception of the risks associated with vaccines. Medical authorities acknowledge that the risk of experiencing severe health problems related to immunization is much less than the risk of developing severe health problems from the diseases that vaccines protect against. Before vaccines, millions of Americans each year developed diseases such as measles, polio, diphtheria, pertussis, tetanus, mumps and rubella. Thousands died and many more suffered permanent disability. Vaccinations have reduced these diseases by 99% or more.

While no vaccine is 100% safe, unsubstantiated claims about vaccine safety, including its perceived link to autism, could result in children not being vaccinated. Such actions will only hurt our children by increasing their risk of developing debilitating and sometimes fatal vaccine-preventable diseases, such as whooping cough, measles and meningitis, among others.

The Immunization Education and Action Committee (IEAC) of the National Healthy Mothers, Healthy Babies Coalition (HMHB) supports the continued use of federal funds to determine the cause or causes of autism and increased research to improve the safety of all vaccines – those on the market and in development – to ensure that our children are being given the safest and most effective vaccines available. We support efforts to strengthen the US Food and Drug Administration's drug surveillance systems to track adverse events that may be caused by vaccines. However, we also support continued administration of vaccines according to the recommended schedule.

The widespread use of childhood immunizations to prevent disease has been one of the most successful public health achievements of the last 100 years, saving millions of lives and increasing the lifespan of much of our population. At a time when childhood immunizations are at an all-time high, exaggerating the perceived risks of vaccines will only weaken our country's successful immunization program at the expense of our children.

For more information, contact Dena Wichansky, IEAC Program Manager, at (703) 836-6110, ext. 228.

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NACCHO

1100 17th Street, NW, Second Floor
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(202) 783-5550 (202) 783-1583 (Fax)

National
Association of
County and City
Health Officials

March 29, 2000

The Honorable Henry Waxman
Ranking Member
House Committee on Government Reform
B-350A Rayburn House Office Building
Washington, DC 20515

RE: Vaccine Safety Hearings

The National Association of County and City Health Officials (NACCHO) is deeply concerned that Congressional hearings on vaccine safety are creating a false perception of the risks associated with vaccines. While no vaccine is 100 percent safe, unsubstantiated claims about vaccine safety, including its perceived link to autism, may cause parents not to vaccinate their children, thus jeopardizing the health of millions. Exaggerating the actual risks of vaccines will only hurt our children by decreasing immunization rates, thereby increasing their risk of developing debilitating and sometimes fatal vaccine-preventable diseases, such as whooping cough, measles and meningitis, among others.

The nearly 3,000 local public health agencies – in cities, counties and towns - have played a crucial role in ensuring that children, adolescents and adults are vaccinated according to recommended schedules. In fact, 93% of local public health agencies provide, contract, or contribute resources to childhood immunizations. Local public health agencies often serve as safety net immunization providers for children whose families have no other access to preventive health services. Local public health agencies have implemented many strategies, including outreach and public education, to raise and sustain vaccination coverage levels in their communities.

The widespread use of childhood immunizations to prevent disease is one of the most successful public health achievements of the last 100 years, saving millions of lives. One result has been that, because vaccine-preventable diseases have become relatively rare, the health threats they pose no longer seem real. The days when thousands of children were stricken with paralyzing poliomyelitis have been forgotten by most. Some now hold an erroneous belief that the risks of vaccines, both real and perceived, have become greater than the risks of acquiring the diseases themselves..

Local public health agencies have witnessed oubreaks of measles and other preventable childhood diseases when immunization rates have declined. They understand how easily low immunization rates can lead to increased illness, disability and death. To prevent a tragic resurgence of preventable diseases, communities must maintain strong immunization programs that have the support of parents and the public.

NACCHO urges continued strong support for childhood immunization programs, as well as more research and increased surveillance for adverse reactions to ensure that unsafe vaccines never become a public health concern. At a time in our history when vaccine-preventable diseases are on the decline in the United States and childhood immunization rates are at an all-time high, exaggerating the perceived risks of vaccines will only threaten the successes of our country's immunization program at the expense of our children.

Sincerely,

Stephanie B.C. Bailey, MD, MSHSA
President

Contact: Donna Brown
202-783-5550

Testimony for the record
Trish Parnell
Director
PKIDs
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pkids@pkids.org

My name is Trish Parnell. I'm the director of PKIDs, a national nonprofit for parents of kids living with chronic, viral infectious diseases. One of our primary goals is to ensure the health of the world's children through global immunization.

Every parent of a child living with a vaccine-preventable disease will tell you that they'd do or give anything to turn back the clock and have their child immunized. These diseases are preventable, and when a parent faces the fact that their child is now irrevocably affected by such a disease, it's devastating.

PKIDs is committed to protecting our nation's children against diseases that have life-long effects on their health and development. As the committee looks at autism today, we voice our support for more resources for autism research while stressing that there is no scientific evidence linking autism to immunization.

We believe there is a long way to go in understanding autism. As a nation, we cannot ignore the need for research to find a cure for this severe and very prevalent neurological disorder. Autism affects more than 400,000 families and costs the nation over 13 billion dollars a year - it deserves as much public attention and research as other childhood diseases.

Although autism is currently the third most common developmental disorder, it receives less than five percent of the funding for research of other childhood diseases, like multiple sclerosis and cystic fibrosis. Funding for research into diseases such as autism is an integral part of finding a cure.

While PKIDs advocates for additional resources for autism research, it does not condone the spread of false and misleading information linking autism to childhood vaccination. PKIDs strongly encourages parents to continue immunizing their children with scientifically proven safe and effective vaccines.

Today's high immunization rates protect us from outbreaks of measles, rubella, diphtheria and polio. If we stop vaccinating, costly outbreaks of these vaccine-preventable diseases would return as surely as spring follows winter with devastating consequences for some families.

Over the past 50 years, vaccines have gained control over or virtually eliminated diseases that used to be very common in the U.S., including measles, diphtheria, polio, smallpox, rubella, Hib meningitis and mumps.

But, other diseases such as hepatitis B, varicella and pneumococcal meningitis are still common, resulting in serious illness for many families. In fact, even in the U.S., where immunization rates are the highest, approximately 1 million pre-school children are not adequately protected against potentially disabling or fatal diseases that can be prevented by immunization.

We urge everyone to keep kids safe with available vaccines and to search for every spare dollar which can be put toward finding a cure for autism, hepatitis B and C, HIV and other diseases and disorders which negatively affect the quality of our children's lives and sometimes even end their lives.

Thank you.

Statement by the American Medical Association on the Connection Between Autism and Vaccines

Resources on Infectious Diseases

Resources on Infectious Diseases

Vaccines Do Not Cause Autism

Congress to examine vaccination's alleged link to autism

On April 6, 2000, the Committee on Government Reform, chaired by Representative Burton, will be holding a Hearing on autism. As part of this hearing, the Committee will be obtaining testimony on the alleged causal association between vaccinations--in particular the measles/mumps/rubella (MMR) vaccine--and autism. Immunization is perhaps the most significant public health story of this century, and the AMA remains committed to maintaining the major public health benefits of vaccinations. The AMA believes that critical public health decisions must be made on the basis of well-conducted scientific research and established scientific fact, and not on anecdotal case reports. Thus, the AMA has prepared the following information highlighting the absence of scientific evidence linking vaccinations to autism.

Scientific data does not support a causal association between vaccination and autism

To date, there have been no convincing scientific data that links any vaccine to autism or any other kind of behavioral disorder. Wakefield and co-workers published the only evidence that suggests a causal association between vaccines and autism in the *Lancet* in 1998. Specifically, based on data from 12 patients, Wakefield suggested that the measles/mumps/rubella (MMR) vaccine may have been responsible for bowel problems that may lead to a decreased absorption of essential vitamins and nutrients, which could have then resulted in developmental disorders like autism. However, no scientific analyses were presented to substantiate this claim, and factors such as referral bias and the small sample size were not considered. Additionally, the theory that autism in the 12 patients is caused by poor absorption of nutrients is not supported by the study's own clinical data. At least 4 of the 12 patients had behavioral problems prior to the onset of symptoms of inflammatory bowel disease, the supposed mechanism for autism after the MMR vaccination. Most significantly, a later publication from Wakefield's group has shown that patients with inflammatory bowel disease were negative for measles virus indicating that measles virus is not responsible for inflammatory bowel disease.

On the other hand, much scientific data exist to show no causal association between the MMR vaccine and autism. A large study by Taylor and coworkers also published in the Lancet in 1999 showed that while the number of autism cases have been increasing in London, the increase was not associated with the introduction of the MMR vaccine. The study also showed that in autistic patients, vaccination did not result in earlier expression of symptoms, and, most significantly, the incidence of autism was the same in children who received the MMR vaccine when compared to children who did not receive the vaccine. Thus, there is no causal association between the MMR vaccine and autism. Additionally, studies also exist to indicate no causal association between the diptheria/pertussis/tetanus (DPT) vaccine and autism and in 1990 the Institute of Medicine has indicated that is no evidence to demonstrate a causal relation between the DPT vaccine and autism.

The theoretical causes of autism rule out vaccination as a causal factor

Autism is a chronic developmental disorder. Its main characteristics are problems in social interaction, communication, and restrictive and repetitive interests and activities. The causes of autism are unknown in most cases. However, recent scientific studies indicate that autism may be a genetically based disorder that occurs before birth. A working group convened by the National Institutes of Health concluded in 1995 that autism is a genetic condition. A recent article in the February 2000 issue of Scientific American provides a nice summary of these theories. This article concludes, "The causes of this baffling and debilitating behavioral disorder may lie in early embryonic development, when malfunctioning genes could produce subtle changes in the structure of the brain stem." Thus, it is extremely unlikely, if not impossible, that vaccination is a causal factor for autism.

The National Alliance for Autism Research (NAAR) States That Vaccines Are Not Causally Associated With Autism

The National Alliance for Autism Research (NAAR), the leading national organization dedicated to finding the causes, prevention, effective treatment and, ultimately, cure of autism, published in their Fall 1998 newsletter (the NAARRATIVE), an article titled "The ABCs of MMRs and DTPs: Is there an association between vaccination and autism?" This article states, "...there has been little if any scientific evidence to substantiate an association between vaccination and autism," and that "The lack of data to support a connection between vaccine and autism makes sense given the increasing body of information concerning when the neurobiological differences associated with autism first occur. The preponderance of evidence tells us that autism happens to our children before birth, not after."

Other Resources on Autism and Vaccination

The Centers for Disease Control and Prevention (CDC) has a fact sheet entitled "Vaccines and Autism."

The Institute for Vaccine Safety of the Johns Hopkins University has details on studies demonstrating the lack of causality between the MMR vaccine and autism.

The National Network for Immunization Information provides provide the public, health professionals, policy makers, and the media with up-to-date, independent and scientifically valid information related to immunization to help them understand the issues and to make informed decisions.

Posted on 4/3/2000
Content provided by L.J. Tan, PhD, Senior Scientist, Infectious Diseases, AMA.

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MOREHOUSE
SCHOOL OF MEDICINE

Office of the President

April 3, 2000

The Honorable Henry A. Waxman
2204 Rayburn HOB
Washington, DC 20515-0529

Dear Representative Waxman:

I am writing to call your attention to a matter I believe to be of critical importance to the health of our nation's children. The House Government Reform Committee has scheduled a hearing for April 6, 2000, entitled "Autism: Present Challenges, Future Needs – Why the Increased Rates?" that will focus, among other things, on the unsubstantiated link between autism and vaccines, including the measles-mumps-rubella (MMR) vaccine. This hearing already has generated media coverage and is anticipated to generate additional news coverage. I am extremely concerned that this attention may inappropriately prompt parents to forgo their children's immunizations, which will deprive them of the important health protections afforded by vaccines.

As former Secretary for the Department of Health and Human Services, I share the Committee's goal to determine the causes of autism, to identify effective treatments and to find a cure so that all families will be free of the burdens caused by this disease. I also share the Committee's goal of assuring the safety and effectiveness of vaccines being administered to our children. I feel compelled to report to you, however, that the best available science indicates that the development of autism is completely unrelated to use of the MMR or any other vaccine. The National Network for Immunization Information (NNii), upon whose Steering Committee I serve, plans to provide a statement at the hearing to this effect and will submit a list of supporting references. My hope is that you will pay close attention to NNii's statement as they serve as an unbiased voice on immunization issues within the scientific and medical communities.

Because autism is usually diagnosed in children when they are 18 to 30 months old, shortly after children receive many recommended immunizations, some parents may attribute the emerging symptoms of autism to the administration of a vaccine. In fact, the best evidence demonstrates that autism results from complex genetic factors and therefore originates prior to birth, not afterward.

KNOWLEDGE • WISDOM • EXCELLENCE • SERVICE
720 Westview Drive, S.W.   Atlanta, Georgia 30310-1495   Telephone (404) 752-1740

My concern is that this hearing will prompt media attention that will unnecessarily raise questions about immunizations and lead to an erosion in public confidence in immunizations. Should this happen, then children will be at risk of infectious diseases that currently are well controlled as a result of our successful immunization program. A similar autism scare in the United Kingdom three years ago prompted many parents to abandon the UK vaccine program. As a result, many children in the UK have gone without the vaccines administered there. Scientists and public health experts in the UK have since conducted an extensive examination of this matter and, after a systematic review of hundreds of reports from parents and physicians, have concluded that the association between autism and vaccines is unsupported in science and medicine.

Given the many successes being realized in the United States through our own vaccine program in the prevention of measles, mumps and rubella, an event in the U.S. similar to the UK experience would be tragic indeed. It was just a decade ago that the U.S. experienced a resurgence of measles. We experienced more than 55,000 cases of measles and buried 125 children and young adults because of fatal complications. After redoubling our efforts, in the past year the country reported fewer than 100 cases of measles. To avoid a recurrence of this predictable tragedy, I urge you, as a Member of the Government Reform Committee, to do what you can at the April 6th hearing to calm the concerns of any parents who may listen to or read media reports about this hearing so that our children will remain protected from unnecessary harm due to infectious diseases.

I thank you for the opportunity to share my thoughts on this important matter.

Sincerely,

Louis W. Sullivan

Louis W. Sullivan, M.D.
President

Written testimony to the Congress of the United States House of Representatives Committee on Government Reform: Hearing on "The challenges of autism. Why the increased rates?"

Dr. Elizabeth Miller
Epidemiologist and Head of the Immunisation Division
Public Health Laboratory Service
England and Wales

Dr. Paddy Farrington
Lecturer, Department of Statistics
Open University, UK

We are pleased to provide written evidence in relation to the congressional hearing on autism, in particular the issue of whether the condition may be caused by MMR vaccine. Together with Professor Brent Taylor, we have conducted an epidemiological study [1] to test the hypothesis raised by Wakefield and his colleagues [2] that MMR vaccine may cause the onset of autistic symptoms within a few days or weeks of immunisation, particularly the form of the disease which presents with regression. **Our conclusion, based on the findings of our study, is that there is no evidence of a causal association between MMR vaccine and autism.**

In order to test the hypothesis raised by Wakefield it is necessary to measure the rate at which new cases occur (i.e. their incidence) in the defined post vaccination risk period (weeks or months based on the Wakefield paper) relative to the background rate of onset of autism in children of the same age. The statistical methodology that we used is called the case series method and was developed specifically by Dr. Farrington for investigating the relationship between vaccination and subsequent clinical events. The method allows a formal assessment to be made of whether the risk of such an event is greater than expected by chance. We have already published a number of papers on the case series method, both with respect to its theoretical basis as well as its use in detecting real vaccine-associated adverse events. These papers are listed in the Appendix together with a summary of the main findings from these studies. **Our case series method has a proven track record with respect to identifying and measuring a risk of adverse events after various vaccines.**

The critical conditions which must be satisfied for the case series method (or indeed any other epidemiological method) to be valid are as follows:

- first, the method used to obtain the cases must be entirely independent of vaccination history
- second, before the analysis is begun the risk periods which are to be investigated must be specified at the outset. If this is not done and the data sets are just analysed looking for any association whatever the temporal relationship with vaccination, then there is a very real danger that spurious "risks" will be found just by chance.

These two conditions were rigorously followed in our study of the temporal association between MMR vaccine and onset of autism and we fully endorse the evidence submitted to the congressional hearing by our colleague, Professor Taylor, on this study. **We reiterate our previous statement that our study shows no evidence of a causal association between MMR vaccine and autism.**

Moreover, Wakefield has provided no epidemiological evidence in support of such a causal association. The inaccuracies in the graph which he submitted to the Lancet following publication of our paper have been addressed by Professor Taylor in his evidence. However, not withstanding these errors, demonstration of an apparent co-incidence of population trends in the use of MMR vaccine and the prevalence of autism does not, by itself, prove that that there is a causal association between the two. On the other hand, where these is no temporal coincidence between two trends, this is evidence of a lack of causal association between them. **In our study we showed that the increase in the prevalence of diagnosed autism in recent birth cohorts occurred during a time when the coverage of MMR vaccine in the same cohorts has been constant. The rise cannot therefore be related to the use of MMR vaccine.**

Following publication of our paper [1], Wakefield wrote to the Lancet [3] criticising certain aspects of our study. These were addressed in our response to the Lancet [4] and in Professor Taylor's evidence to the congressional committee. Wakefield's main criticism that we "concealed" the fact that the children born before 1987 may have had MMR vaccine in a catch-up was not only epidemiologically irrelevant [4] but also implied intention to deceive on our part. We refrained from responding to the latter imputation in our letter to the Lancet and concentrated on refuting the scientific aspects of his criticism. **We welcome the opportunity here of stating categorically that any allegation of deception or concealment in our Lancet paper is entirely without foundation.**

In Dr. Wakefield's Lancet paper on autism he refers to previous laboratory and epidemiological work on measles virus and measles vaccination both of which he says have been implicated as risk factors for Crohn's disease. He quotes this earlier work in the context of the biological plausibility of the suggestion that the components of MMR vaccine might cause autism. The laboratory work that he quotes used an immunoreactive method [5]. The authors of this paper admit that the positive signals they report, suggesting the presence of a measles antigen, may be an artefact arising from the phenomenon of antigenic mimicry (ie non-specific cross reactions). This has now been shown to be the case with the original immunohistochemical method employed by Dr. Wakefield, who first reported the presence of measles virus in the tissues of patients with Crohn's disease [6]. The positive results he obtained which he claimed showed the presence of measles antigen in tissue from patients with Crohn's disease have now been shown to be non-specific and an artefact arising from immunological cross reactions [7]. Using more specific and sensitive molecular methods neither Dr. Wakefield [8] nor other workers have been able to show the presence of measles virus in the tissues of patients with Crohn's disease [9 - 12]. **The laboratory evidence published to date does not therefore implicate measles virus in Crohn's disease.**

The epidemiological evidence that Wakefield cites in his Lancet paper purporting to implicate measles virus or measles vaccination in Crohn's disease is similarly flawed. He quotes a paper by Ekbom et al [13], of which he is a co-author, reporting that 3 of 4 children whose mothers had measles during pregnancy developed Crohn's disease in later life. This was not a prospective controlled study and was published as an early *ad hoc* report in the Lancet. Three subsequent studies failed to substantiate this putative association. The first, and perhaps strongest, refutation of the Ekbom paper was published by Jones et al in 1997 [14] and was not referenced in the Lancet paper on autism by Wakefield. The study by Jones and his colleagues was a prospective controlled study set up in the 1950s specifically to document the outcome of various viral infections in pregnancy. None of the offspring of 47 women who had measles infection in pregnancy and who were recruited to the UK study at the time of their mother's infection had inflammatory bowel disease when followed up some 33 years later. This compares with 2 cases among the 47 controls recruited at the same time and followed up by similar methods. This clear refutation of the Ekbom hypothesis that measles in pregnancy is a risk factor for Crohn's disease was subsequently confirmed by studies in Denmark and the US [15,16]. **There is therefore no reliable evidence that *in utero* exposure to measles infection is a risk factor for the subsequent development of Crohn's disease and strong evidence that it is not.**

The study quoted by Wakefield in his Lancet paper [2] which purports to show that measles vaccination is a risk factor for Crohn's disease was heavily criticised on epidemiological grounds at the time of its publication and in the subsequent correspondence to the Lancet [17-23]. Later, more robust studies [24, 25], one of which is by Wakefield himself [25], have failed to substantiate this earlier work. **There is therefore no credible epidemiological evidence to support of the view that measles vaccination is a risk factor for Crohn's disease or indeed any other inflammatory bowel disorder.**

In his letter to the Lancet [3] following the publication of our paper on autism [1] Wakefield mentions a recent study from his group [26] as strongly supporting a role for measles virus in chronic intestinal inflammation. To quote from his letter *"The latest of these studies [26] was strongly positive, and was accepted by the MRC".* This is not the case. The epidemiological evidence he reports in that paper was presented in detail by Montgomery and Wakefield to the expert group convened by the MRC on 23rd March 1998. **The conclusion of the MRC group on Wakefield's study was that the findings were not sufficiently robust to allow conclusions to be drawn from them. We agree with this conclusion.**

The absence of an association between inflammatory bowel disease and autism in England [27[or bowel symptoms after MMR vaccination and autism in Finland [28] or autism and MMR vaccination in Sweden [29] adds further support to our study in which we conclude that there is no epidemiological evidence of a causal association between MMR vaccine and autism.

BEST COPY AVAILABLE

References

1. Taylor B, Miller E, Farrington P et al. Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association. Lancet 1999; 353:2026-29.

2. Wakefield AJ, Murch SH, Linnell A et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis and pervasive developmental disorder in children. Lancet 1998; 351: 637-41

3. Wakefield AJ. MMR vaccination and autism. Lancet 1999; 354: 949-50 (corresp)

4. Taylor B, Miller E, Farrington P. MMR vaccination and autism. Lancet 1999; 354: 950 (corresp)

5. Miyamoto H et al J. Detection of immunoreactive antigen, with a monoclonal antibody to measles virus, in tissue from a patient with Crohn's disease. Gastroenterol 1995; 30: 28-33

6. Wakefield AJ et al. Evidence of persistent measles, virus infection in Crohn's disease. J Med Virol 1993; 39: 345-353

7. Iizuka M et al. Immunohistochemical analysis of the distribution of measles related antigen in the intestinal mucosa in inflammatory bowel disease. Gut 2000; 46: 163-169.

8. Chadwick N et al. Measles virus RNA is not detected in inflammatory bowel disease using hybrid capture and reverse transcriptase followed by polymerase chain reaction. J Med Virol 1998; 55:305-11.

9. Haga Y et al. Absence of measles viral genomic sequence in intestinal tissues from Crohn's disease by nested polymerase chain reaction. Gut 1996; 38:211-15

10. Iizuka M et al. Absence of measles virus in Crohn's disease. Lancet 1995; 345: 199 (corresp)

11. Afzal MA et al. Absence of measles virus-virus genome in inflammatory bowel disease. Lancet 1998; 351: 646-47 (corresp)

12. Afzal MA et al. Absence of detectable measles virus genomic sequence in inflammatory bowel disease tissues and peripheral blood lymphocytes. J Med Virol 1998; 55: 293-99

13. Ekbom A et al. Crohn's disease after in-utero measles virus exposure. Lancet 1996; 348: 525-17.

14. Jones P et al. Crohn's disease and measles. Lancet 1997; 346: 473 (corresp)

15. Nielson LLW e al. Exposure to measles in utero and Crohn's disease: Danish register study. BMJ 1998; 316: 196-7

16. Pardi et al. Perinatal exposure to measles virus is not associated with the development of inflammatory bowel disease. Inflammatory Bowel Diseases 1999; 5: 104-06

17. Patriarca PA and Beeler JA. Measles vaccination and inflammatory bowel disease. Commentary. Lancet 1995; 345: 1062-63

18. Farrington P, Miller E. Measles vaccination as a risk factor for inflammatory bowel disease. Lancet 1995; 345: 1362. (corresp)

19. Calman KC. Measles vaccination as a risk factor for inflammatory bowel disease. Lancet 1995; 345: 1362 (corresp)

20. Minor PD. Measles vaccination as a risk factor for inflammatory bowel disease. Lancet 1995; 345: 1362-63 (corresp)

21. MacDonald TT. Measles vaccination as a risk factor for inflammatory bowel disease. Lancet 1995; 345: 1363 (corresp)

22. Miller D, Renton A. Measles vaccination as a risk factor for inflammatory bowel disease. Lancet 1995; 345: 1363

23. Baxter T, Radford J. Measles vaccination as a risk factor for inflammatory bowel disease. Lancet 1995; 345: 1363 (corresp)

24. Feeney M et al. A case-control study of measles vaccination and inflammatory bowel disease. Lancet 1997; 350: 764-66

25. Morris DL et al. Measles vaccination and inflammatory bowel disease in the 1970 British cohort study (abstract in Gut December 1997; oral presentation at United European Gastroenterology Workshop

26. Montgomery SM et al. Paramyxovirus infections in childhood and inflammatory bowel disease. Gastroenterology 1999; 118:796-803.

27. Fombonne E. Inflammatory bowel disease and autism. Lancet 1998; 351: 955

28. Peltola H et al. No evidence for measles, mumps, and rubella vaccine-associated inflammatory bowel disease or autism in a 14 year-prospective study. Lancet 1998; 351: 1327-28.

29. Gillberg C, Heijbel H. MMR and autism. Autism 1998; 2: 423-24

Appendix

The statistical basis and empirical validation of the case series method is given in references 1 and 2 below. The development of the record linkage method for vaccine safety studies is described in references 3 and 4.

Using the case series method with data sets obtained by record linkage, we have measured the risk of a convulsion 6-11 days after MMR vaccine (known to be due to the measles component) and obtained similar estimates to those found in studies in which large cohorts of MMR-vaccinated children have been followed up prospectively from the time of immunisation (5). Similarly, we have shown that DTP (diphtheria/tetanus/whole cell pertussis) vaccine causes hospital admission for convulsion (albeit rarely) within 3 days of immunisation (5), a causal association which has been shown in prospective clinical trials using this vaccine. We have also identified and measured the risk of a convulsion 15-35 days after MMR vaccine, and shown that this was due to one particular mumps vaccine strain that has now been replaced in the vaccines used in the UK (5,6). The risk of a rare blood disorder called idiopathic thrombocytopenic purpura, which causes a characteristic skin rash, has also been shown to be raised after MMR vaccine by the case series method (5,7). For all the above adverse effects the risk from the disease in substantially greater than that from the vaccine.

More recently, we have used our method to investigate convulsions after Hib vaccine and found no evidence of an increased risk in the 0-3 day, 4-7 day or 8-14 day post vaccination period (4). The absence of an increased risk of convulsions after Hib vaccine accords with the effects of the vaccine as shown in prospective clinical trials.

Our case series method has therefore a proven track record both with respect to identifying a risk of certain adverse events from MMR and DTP vaccines as well as showing no evidence of risk for the same events with other vaccines.

References:

1. Farrington CP. Relative incidence estimation from case series for vaccine safety evaluation. Biometrics 1995; 51: 228-35

2. Farrington CP, Nash J, Miller E. Case series analysis of adverse reactions to vaccines: a comparative evaluation. Am J Epidem 1996; 143: 1165-73

3. Nash JQ, Chandrakumar M, Farrington CP et al. Feasibility study for identifying adverse events attributable to vaccination by record linkage. Epidem Infect 1995; 114: 475-80

4. Miller E, Waight P, Farrington P. Safety assessment post licensure. Dev Biol Stand 1998; 95: 235-43

5. Farrington P et al. A new method for active surveillance of adverse events after diphtheria/tetanus/pertussis and measles/mumps/rubella vaccines. Lancet 1995; 345: 567-69.

6. Miller E et al. Risk of aseptic meningitis after measles, mumps, and rubella vaccine in UK children. Lancet 1993; 34: 979-82

7. Miller E, Waight PA, Farrington P. Andrews N, Stowe J, Taylor B. Idiopathic thrombocytopenic purpura and MMR vaccine (in press)

TESTIMONY OF DR. ERIC FOMBONNE

I am Dr. Eric Fombonne, Reader in Epidemiological Child Psychiatry at the Institute of Psychiatry- King's College London (U.-K.), and Consultant Child and Adolescent Psychiatrist at the Maudsley Hospital (London, U.K.) for the Pervasive Developmental Disorders Service. I have extensive clinical and research experience in autism and related disorders.

I am unable to testify in person at this hearing but appreciate the opportunity to testify in writing the following comments for the Committee.

Recent investigations of children with pervasive developmental disorders (a generic term for autistic disorder) who were referred to a gastroenterological unit because of gastrointestinal symptoms have suggested that a loss of skills had occurred in the children after the combined measles, mumps, and rubella (MMR) immunization or after measles infection. All children had histological or biological abnormalities suggestive of rather nonspecific inflammatory processes which casted doubts on the putative links with the measles virus. Moreover, in the absence of a control group, however, it is difficult to draw meaningful conclusions from these observations. In fact, the linking of measles exposure to the Aonsete of autism relied, to a large extent, on the apparent temporal connection between the first symptoms of autism and an MMR immunization shot. However, there were no details on how such precise estimates had been obtained from parents and there was no independent corroborative evidence. Most professionals in the field of autism and most parents would recognize that it is extremely difficult to date the onset of the first autistic symptoms in a child with accuracy, either at the time or retrospectively. Parents recognize the first autistic abnormalities in their children before the first birthday in about 40% of cases. This means that, for the majority of autistic children, parents become concerned between the first and third birthday, and usually during the second year of life with a large group of children giving first developmental concerns in their third trimester of life. Any event (biological, social, etc.) occurring during the third semester of life will therefore coincide with the onset of autism in autistic children. MMR immunization is usually given between 12 and 15 months of age in the UK, and the onset of autism and immunizations will therefore be linked because of the connection between the particular timing of immunization programs and the natural history of symptom development in autism. This temporal association, however, is coincidental and must not be taken as evidence for a causal association.

Other arguments are therefore necessary to suggest a causal link (as opposed to a mere temporal association) between the two events. However, there is no evidence from case control studies that measles infections are a strong risk factor for autism; similarly, epidemiological surveys have not identified measles infections, or their rare complications (such as subacute sclerosing panencephalitis), as common background medical conditions in autism. Indeed, in a review of 27 epidemiological surveys published in the English language that we performed recently and where possible causal medical disorders were investigated in about half of the studies, no mention was ever made of wild measles infection or of its complications as being associated with the onset of autism in very large, representative samples of autistic children.

In the UK, MMR immunizations were introduced only in 1988 and this provides a theoretical opportunity to link changes in rates of autism in the population with the introduction of a systematic immunization programme. However, the epidemiological evidence for a real increase in the incidence of autism is thus far largely lacking. It is useful, here, to distinguish two epidemiological measures: prevalence and incidence. Prevalence, or prevalence rate, is a measure of the proportion of the population affected by a disorder at a given point of time. Incidence is a measure of the number of new cases of a disease occurring in a population over a period of time. Only incidence data can inform us about causal factors associated with rates of a disorder in a population. In the field of autism, no epidemiological study has ever yielded incidence rate estimates; this is because autism, and related disorders, are too rare, and because the diagnostic boundaries of autism were very difficult to operationalize for a long time. Thus, epidemiologists have available to them only prevalence estimates of autism in various countries or regions, and usually at different points in time.

Under strict methodological circumstances, prevalence rates derived from epidemiological studies could be used to indirectly assess changes in the incidence of the disorder. This would be achieved if prevalence rates can be meaningfully compared at two different points in time, or in successive birth cohorts. For such a comparison to be meaningful, demonstration should be made that the concepts, definitions and diagnostic assessment of autism-spectrum are strictly comparable across studies or birth cohorts, that the methods used to identify cases in populations are the same, that the age groups compared are similar, and that the areas surveyed are comparable regarding their population structure and migration out and in the area under study. No study has achieved such a tight control of confounding factors in making such comparisons. The surveys performed in Europe, and notably in Sweden and in France, which attempted to address the issue of a secular change in the incidence of autism have concluded that either there was no detectable increase in prevalence rates over time once definitions and methods were held constant across surveys, or that increasing rates over time could be accounted by changes in the detection of autism in populations or changes in the concepts and diagnostic definitions of autistic spectrum disorders.

Data have recently been published from various educational departments or centers (for instance, in California) which portray alarming upward trends in numbers of autistic children registered in the corresponding databases. However, these data are not epidemiological in nature and they are susceptible to various biases and confounding factors. Firstly, these data are just numbers of children as opposed to rates. Only rates would be used by epidemiologists as they incorporate in the measure of disease occurrence a meaningful description of the underlying population. Numbers could change as a result of changes in the composition of the population and they cannot be used without relating them to population denominators. Secondly, no attempt was made in these series to control changes in the diagnostic concepts and definitions. The diagnostic classification in use in the USA (DSM) has changed three times over the last 20 years, in 1980, 1987 and 1994. Changes to the classification systems and diagnostic criteria were substantial for children with autistic conditions. The same children who did not meet criteria for autism before 1987 met criteria for autism thereafter, and so on. Reporting time trends in such data without taking these definitional changes into account is not good practice. Thirdly, over the years, there has been an increasing recognition of autistic conditions both in the lay and professional publics. This, in turn, has led to earlier identification of autistic children who are now diagnose at a much earlier age in most countries. In itself, this trend towards an earlier age at diagnosis has contributed to an increased prevalence of diagnosed autism spectrum conditions, overall in the population, and especially amongst young children. Thus, even though the prevalence pool of children with autism might have remained the same in the population, this trend towards an earlier diagnosis will have contributed to an increase in the number of notifications to agencies, more pressure on professional assessment centers and a corresponding perception that there is more autism now than before. This would, however, not necessarily be the correct interpretation. Fourthly, the same data also showed upward trends in several childhood handicaps other than autism, casting doubts on the specificity of these trends for autism and suggesting a common artefact in the reporting statistics. For all these reasons, these statistics cannot be interpreted as indicative of a secular increase in the incidence of autism.

Therefore, there are no solid epidemiological data to support the hypothesis of an increased incidence of autism, the epidemiological measure of crucial scientific interest. On the other hand, prevalence rates have tended to be higher in the last 15 years but this mostly reflected an improved recognition of autism in the population surveyed as well as a progressive broadening of the definition of the disorder. Thus, it is not correct to interpret the upward trend in rates of prevalence as evidence that the incidence has increased.

Similarly, there are no robust epidemiological studies linking rates of autism to the relatively recent use of the combined MMR vaccine in immunization programs in some countries. One UK study which specifically tested for an association between rates of autism in North London and the introduction of MMR immunization in 1988 failed to detect an association. Beyond the putative link between measles viruses/immunizations and autism, it has also been argued that measles viruses were responsible for the increased incidence of inflammatory bowel diseases and Crohn=s disease. If measles viruses were implicated in both autism and inflammatory bowel diseases, then, surely, there should be an association between autism and inflammatory bowel disease. When tested in two large samples of subjects with autism, this hypothesis was unsupported. Furthermore, inflammatory bowel disease and Crohn's disease were not reported in any of the 27 epidemiological surveys of autism conducted from 1966 to 2000 worldwide.

There is a natural tendency for all of us to seek explanations for events that are unpredictable, painful, and unexplained, such as the appearance of autistic symptoms in a young developing child. Perhaps this drive is even more pronounced in the parents of those children who experience a regression of skills in the second year of their life, as seen in up to 25% of autistic children. The possibility of such a regression in the devlopment of autistic children has been known for a long time, and much before the introduction of combined MMR vaccines. In the past, other reasons have been sought to explain these losses of skills; birth of another child, moving home, hospital admission, or even a simple otitis media. While keeping an open mind on causation and developing new hypotheses are certainly necessary, an important task of professionals is to remain sceptical about claims of causal associations which fall short of strict scientific criteria.

Sincerely,

Dr. Eric Fombonne

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A Statement from Executive Director Mohammad N. Akhter, MD, MPH
April 6, 2000

The American Public Health Association (APHA) expresses its strong and continued support for universal immunization against vaccine-preventable diseases. Immunizations have been proven to be among the safest and most cost-effective health measures ever implemented. For every dollar spent on a measles-mumps-rubella vaccine, more than $16 is saved in direct medical costs (1). Similarly compelling cost-benefit data exists for other vaccines, and they reflect not only dollars saved, but also unnecessary suffering and death prevented.

A recent past issue of the *Morbidity and Mortality Weekly Report* describes the toll taken on America's people before vaccinations were widely available:

> In 1900, 21,064 smallpox cases were reported, and 894 patients died. In 1920, 469,924 measles cases were reported, and 7575 patients died, and 147,991 diphtheria cases were reported, and 13,170 patients died. In 1922, 107,473 pertussis cases were reported, and 5099 patients died (1).

By contrast, in 1998 there was one case of diptheria, 6,279 cases of pertussis, 89 cases of measles and none of smallpox (2). These remarkable reductions in rates of illness and death are attributable to immunization campaigns.

Public health professionals understand that a very small percentage of the population may experience allergic responses or other negative health effects from vaccinations. Long ago, APHA called for the establishment of a national compensation system to alleviate the financial burden of such events. Furthermore, the Association continues to advocate the highest safety standards in vaccine development, manufacture, and distribution, in order to limit such potential adverse effects. These efforts must include research directed to the elimination of the rare unfavorable reactions to immunizations.

In spite of science's best efforts, a small number of reactions may still be experienced. These occasions, like any adverse health effect, are truly devastating for those affected. However, it is important to remember that serious consequences will result for many more people if we reduce our immunization activities. Vaccine-preventable diseases can cause widespread blindness, deafness, brain damage, mental retardation, heart defects, sterility, miscarriage, paralysis, and death.

Advancing the Public's Health Since 1872

Taking into account that the benefits of immunization against childhood diseases far outweigh the risks, we commend national policymakers for their ongoing support for universal immunization. Federal funding that provides grants to states for immunization efforts is vital and has shown dramatic results. In years where funding has been increased, there has been an expansion of the total number of two-year-olds who were fully immunized from 50 percent in 1993 to 78 percent in 1996.

APHA strongly supports efforts to eliminate the scourge of communicable diseases through immunizations and other means throughout the world.

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(1) "A Cost-Benefit Analysis of the Measles-Mumps-Rubella (MMR) Vaccine", Battelle, 1994.
(2) "Achievements in Public Health, 1900-1999: Impact of Vaccines Universally Recommended for Children – United States, 1990-1998", *MMWR*, April 2, 1999.

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Date: March 29, 2000

Chairman Dan Burton
Committee on Government Reform
2157 Rayburn House Office Building
Washington, DC 20515

Dear Chairman Burton:

I am pleased that you are holding hearings on "The Challenge of Autism" on April 6, 2000. We need broad public recognition of the significance of this condition and adequate support for additional research on its causes, prevention and treatment. Having spent four decades studying the etiology, pathogenesis, diagnosis and management of autism, I regret that travel commitments will prevent my attending the hearings. I do want to comment on several issues that currently may be sources of confusion and will appreciate your including my letter and the materials in the hearing record.

1. Autism is a behaviorally defined developmental disorder of the brain. The best available evidence views the autism spectrum disorders as developmental disabilities. The causes of autism are multiple, but complex genetic factors play the dominant role in its causation. The dysfunction reflects developmental pathology beginning early in intrauterine life. (See Kemper, TL and Bauman, M.L. Neuropathology of infantile autism. Journal of Neuropathy and Experimental Neurology 1998; 57:645-652. Rodier,P. Scientific American, January, 2000). Brains examined thus far (many too few of them!) Have failed to reveal evidence for an infection or inflammation, but point to cellular abnormalities going back to early pregnancy.

2. Since behavior patterns suggesting autism may first be appreciated by parents and clinicians during the second year of life, some have attempted to attribute these emerging symptoms to administration of the combined Measles-Mumps-Rubella vaccine. Allegations that vaccination causes autism represent unsubstantiated claims which have not been supported by credible science (e.g., Taylor et. al.: Lancet 1999; 353: 2026-2029)

3. Yes, there is need for continuing research on causes, prevention and treatment of autism. In the meantime, it would be tragic if parents avoided fully immunizing their children for fear of causing autism. In fact, rubella during pregnancy, once a known intrauterine cause of brain damage leading to autism, has been virtually eliminated in the United States because of our national immunization programs. Measles had the potential of causing profound damage to the brain, leaving as many as 1/1000 children profoundly retarded and cerebral palsied, and in some 1/50,000 it causes, often after many years, a devastating progressive dementia called SSPE that may be fatal.

I enclose a Medical Progress article I wrote for the *New England Journal of Medicine* in 1997. Dr. Rodier's article, referenced above, updates some basic scientific advances completed since that review. Also enclosed is a synopsis of my curriculum vitae with references to a book we published on one of the largest NIH funded studies of preschool children with autism ever carried out, as well as to some of my articles you or your staff may find helpful. If I may be of service in any way, please let me know.

Sarah Despres -
Just to make sure you got it

Sincerely yours,

Isabelle Rapin, M.D.
Professor Neurology and
Pediatrics (Neurology)

NNii

National Network for
Immunization Information

99 Canal Center Plaza, Suite 210 • Alexandria, VA 22314 • tel: 877-341-6644 or 703-299-0430 • fax: 703-299-0204

April 4, 2000

The Honorable Dan Burton
Chairman, House Government Reform Committee
2157 Rayburn House Office Building
Washington, DC 20515

Re: The National Network for Immunization Information's Statement for the House Government Reform Committee's April 6 Hearing on "Autism: Present Challenges, Future Needs–Why the Increased Rates?"

Dear Mr. Chairman,

Thank you for the opportunity to provide a statement for the official record of the House Government Reform Committee's April 6 hearing on autism. We wish to comment on one aspect that will be addressed at the hearing: the purported link between the measles-mumps-rubella (MMR) vaccine and autism.

The National Network for Immunization Information (NNii) was established in 1998 to provide the public, health professionals, policy-makers and the media with up-to-date, scientifically valid information related to immunization for the purpose of helping them understand the issues and make informed decisions. An organization of physicians, nurses and other health professionals, NNii serves as the voice of science and medicine on immunization issues.

Because autism is usually diagnosed in children when they are 18 to 30 months old, shortly after children receive many recommended immunizations, some parents may attribute the emerging symptoms of autism to the administration of a vaccine. In fact, the best available science indicates that the development of autism is completely unrelated to use of the MMR or any other vaccine (see attached list of references and websites). Evidence shows that autism results from complex genetic factors and therefore originates prior to birth, not afterward. There has been little, if any, scientific evidence to substantiate an association between vaccination and autism.

We have full sympathy for every child and family burdened by autism and support aggressive research into the causes, prevention and treatment of autism. We also feel it is our obligation to make clear that the current scientific evidence shows that autism is not related to immunizations.

Please feel free to call on us for additional information.

Sincerely,

Bruce G. Gellin, M.D., M.P.H.
Executive Director

cc: House Government Reform Committee

Partners Infectious Diseases Society of America • Pediatric Infectious Diseases Society • American Academy of Pediatrics • American Nurses Association
Co-Chairs Samuel L. Katz, MD, Professor Emeritus of Pediatrics, Duke University • Louis W. Sullivan, MD, President, Morehouse School of Medicine
Director Bruce G. Gellin, MD, MPH, Department of Preventive Medicine, A-1124 Medical Center North, Vanderbilt University, School of Medicine, Nashville, TN 37232-2637

References

Bedford H, et al. Autism, inflammatory bowel disease, and MMR vaccine. Lancet. 1998; 351(9106):907; discussion 908-9.

Birmingham K, et al. Reactions to MMR immunization scare. Nat Med. 1998; (5 Suppl):478-9.

Bower H. New research demolishes link between MMR vaccine and autism. BMJ. 1999; 318(7199):1643.

DeStefano F, et al. Autism and measles, mumps and rubella vaccine: No epidemiological evidence for a causal association. J Pediatr. 2000; 136(1):125-6.

DeStefano F, et al. Negative association between MMR and autism. Lancet. 1999; 353(9169):1987-8.

Evidence to support current policy on MMR vaccination sent to doctors in the United Kingdom. Commun Dis Rep CDR Wkly. 1998; 8(14):123,126.

Fall in MMR vaccine coverage reported as further evidence of vaccine safety is published. Commun Dis Rep CDR Wkly. 1999; 9(26):227, 230.

Fombonne E. Are measles infections or measles immunizations linked to autism? J Autism Dev Disord. 1999; 29(4):349-50.

Fombonne E. Inflammatory bowel disease and autism. Lancet. 1998; 351(9107):955.

London E, Johnson C (editor). The ABCs of MMRs and DTPs: Is there an association between vaccination and autism? NAARRATIVE. 1998; Number 3, Fall.

MMR vaccine is not linked to Crohn's disease or autism. Commun Dis Rep CDR Wkly. 1998; 8(13):113.

Peltola H, et al. No evidence for measles, mumps, and rubella vaccine-associated inflammatory bowel disease or autism in a 14-year prospective study. Lancet. 1998; 351(9112):1327-8.

Roberts R. MMR vaccination and autism 1998. There is no causal link between MMR vaccine and autism. BMJ. 1998; 316(7147):1824

Rodier P. The early origins of autism. Scientific American. 2000; 282 (2):56-63.

Taylor B, et al. Autism and measles, mumps and rubella vaccine: No epidemiological evidence for a causal association. Lancet. 1999; 353 (9169):2026-9.

Websites with Information on MMR and Autism

American Academy of Pediatrics, http://www.aap.org/new/immpublic.htm
American Medical Association, http://www.ama-assn.org/med-sci/immunize/vacautism.htm
Centers for Disease Control and Prevention, http://www.cdc.gov
National Alliance for Autism Research, http://www.naar.org
National Institutes of Health, http://www.nih.gov
National Network for Immunization Information, http://www.immunizationinfo.org

National Network for Immunization Information
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1ST STORY of Level 1 printed in FULL format.

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The Independent (London)

April 4, 2000, Tuesday

ION: NEWS; Pg. 6

TH: 447 words

LINE: STUDY OF THREE-IN-ONE VACCINE FINDS NO EVIDENCE IT CAN CAUSE AUTISM

NE: Steve Connor Science Editor

DOCTORS WHO investigated the health risks of the three-in-one measles, mumps
rubella (MMR) vaccine have found no evidence to suggest it can cause
sm in children.

A group of medical specialists brought together by the Medical Research
cil rejected claims made in 1995 and 1998 that the vaccine is linked with
sm and bowel disease.

The subsequent panic caused a serious fall in childhood vaccinations,
ing fears of a measles outbreak that could do more harm than the supposed
the vaccine.

Professor Alan McGregor, of King's College London, who chaired the
ittee, said the specialists looked at all the evidence that is published or
t to be published, as well as interviewing senior scientists, but still
ed to find a link between vaccinations and autism.

The committee also interviewed Andrew Wakefield, the consultant at the Royal
Hospital in London whose research triggered the scare over the MMR vaccine
r it was published in The Lancet.

Professor McGregor said the committee found the research data published in
Lancet was insubstantial and should not have been used to support claims
the vaccine causes autism. "The reality is that the Lancet research
ated a huge amount of coverage and caused a lot of damage. I hope the
r sees fit to comment on our report," Professor McGregor said. "Without
the potential damage done by these claims is enormous."

esearch published last year on 498 autistic children by a separate group at
oyal Free Hospital, led by Professor Brent Taylor, found no association
the MMR vaccine.

he researchers said the rise in autism, which began in 1986 before the
duction of the MMR vaccine, is probably due to the condition being better
nised and diagnosed than in the past.

he research council announced yesterday that it will fund the biggest study
nto autism, led by Professor Andrew Hall of the London School of Hygiene
ropical Medicine. It will investigate the possible causes of this
rious condition, where children find it difficult to develop normal social
ionships. The research will involve a study of the health records of 2

ion people to see if birth problems or viral infections in the womb may play le. The study will also look at vaccinations.

Isobella Thomas, one of the many parents of autistic children who believe MMR vaccine was responsible, says she is not convinced by Professor egor's findings.

"We know 100 per cent that our children are vaccine damaged. Within hours of r jabs, two of my children reacted and now have a new form of autism," Mrs as said.

UAGE: ENGLISH

-DATE: April 4, 2000

Mr. WAXMAN. I thank all the witnesses who are here today for appearing. I know how difficult it is for some of them to be here, how hard it is to share their pain, and how much they want their testimony to be a way for us to understand that we in the Congress must do everything we can, consider all theories, get to the truth about autism, what causes it, what we can do to treat it, and how we can prevent it. I see that as our job today, and I look forward to the testimony and learning from the witnesses who are here to share their perspectives with us.

Thank you, Mr. Chairman.

Mr. BURTON. Thank you, Mr. Waxman.

Mrs. Morella.

Mrs. MORELLA. Thank you, Mr. Chairman. I appreciate your effort to hold this important hearing on autism, and I look forward to hearing the testimony of the witnesses.

I come to this hearing today with an open mind, ready to listen carefully to the testimony of the witnesses. Autism and its associated behaviors have been estimated to occur in as many as 1 in 500 individuals. Over 500,000 people in the United States today have some form of autism. The estimated prevalence rate of autism now places it as the third most common developmental disability—more commonly occurring than Down Syndrome.

Mr. Chairman, in your opening statements, you mentioned that there was a 513 percent increase in my State of Maryland between 1993 and 1998, and I notice that the first witness on our first panel, Mr. Curtis, is from Maryland.

Unfortunately, there is almost no existing data on causes or links to causes of autism in children. I am very concerned with these striking statistics. I am most concerned with the lack of information and the confusion surrounding the issue of vaccines and their relationship to autism.

I hope that today we can come closer to discerning what the appropriate steps are for this committee and for Government to take. I hope to learn from testimony that will make this committee better understand where we need to focus research dollars, be it through vaccines, genetic or environmental factors, and the question of why is autism four times more prevalent in boys than in girls. I hope to get some sense of what further studies are needed so that we can accelerate research on autism.

There is no question in my mind that this is an issue of high priority and that more studies are needed. That is why I wrote to our Representative John Porter, who chairs the House Subcommittee on Appropriations for Labor and Health and Human Services, requesting an increase in funding for autism epidemiology research at the National Center for Environmental Health within the Centers for Disease Control and Prevention, an appropriation of $1.5 million for the CDC to expand its epidemiology activities in autism from two isolated studies to a more national scope.

An increase in funding for autism epidemiology research in 2001 will enable CDC to expand monitoring efforts to other parts of the country. This will allow them to better understand the prevalence of autism spectrum disorders—information which is necessary to eventually discover prevention, treatment, and a cure for autism.

I think that the choice of this ribbon with its puzzle pieces as the symbol of autism, with the heart in the center, is most appropriate.

I yield back and look forward to hearing from the witnesses.

Mr. BURTON. Thank you, Mrs. Morella.

Mrs. Chenoweth-Hage.

Mrs. CHENOWETH-HAGE. Thank you, Mr. Chairman.

I can hardly begin to thank you enough for holding this hearing. It is astounding to see all of these people who have come from all over the Nation, and I understand, Mr. Chairman, that you have arranged for two overflow rooms, and I noticed that the hall was packed when I came in.

I rarely ask to make an opening statement, but I am unable to overstate the importance of this particular issue, and I look forward to hearing the testimony from the witnesses today and learning more.

Mr. Chairman, oftentimes, I focus on the larger issues at hand when I address the committee, but I too am the grandparent of an incredibly handsome autistic child—an incredible boy. I cannot overemphasize how much autism affects education and family cohesiveness in the most loving of families. All of these are irretrievably affected when autism is discovered in one's own family.

Mr. Chairman, when Timmy was born, neither my daughter nor my son-in-law knew that he was autistic. They did not have a clue. He was the youngest of four children, so his parents thought they knew what to expect in raising a baby. It was only later that they realized that there was something very different about Timmy. When he was diagnosed with autism, we were all worried and saddened. How would our family deal with this? How could he be educated, and how could we best provide for his future? How could, how could how could? And it went on.

We had hundreds if not thousands of questions. We were shocked and frightened and worried and relieved to know what it was, all at the same time. At the same time, none of us knew what the future held, and the questions kept coming.

That is why I am so very grateful to you, Mr. Chairman, for your courage and willingness to deal in areas that the Congress usually is not willing to open its mind to.

Timmy is now 8 and is a beautiful young boy whom we are all immensely proud of. However, I cannot understate the challenges that our family still faces. Parents are desperate to find an answer to their questions. They want so much for their children to have integrative and communicative lives. Oftentimes, they feel at a loss, almost desperate, in trying to find answers to their questions. Many of my family's questions still remain. Day after day, we still search for answers. It is an overriding concern with all of us.

While our questions are not all easily answered, even the beginning of the questions, we do somehow manage to look toward a brighter future for Timmy than we ever thought possible after his initial diagnosis. He was a gifted child in a number of areas, particularly music. But we still want to learn how to unlock the full potential of his future.

All too often, people will write off such potential, but it is there. We are all sure of it. You can literally look in his eyes and see it.

Mr. Chairman, autism is a very strange disorder. When Timmy was diagnosed, we were told that medical science did not know the cause of it. We were told that Timmy had about a 4 percent chance of leading a normal life, depending on his IQ. They thought autism was probably genetic, but they really just were not sure.

After much research, we discovered his current schooling program, which is based on extensive research done by Dr. Iver Lovass of California. At first, quite simply, we encountered a vacuum of knowledge when it came to autism, and that shocked me. However, what shocked me even more was learning that the rate of autism has increased over the past several years, and the statistics which you show today, Mr. Chairman, are incredibly shocking.

I continue to be surprised when I discover that some studies have found preliminary evidence of a link between autism and vaccines, and evidence linking dietary health to autism. Vaccines and dietary health are issues that I have been very interested in for some time now, and I look forward to hearing from the witnesses who will address these links.

Mr. Chairman, we understand from the research that was the foundation of Dr. Lovass' program, "Ready, Set, Go," that the chances of Timmy leading a normal life rose from 4 percent to nearly 20 percent, and this is based on the intensive behavioral intervention program developed after decades of research by Dr. Lovass. You can imagine the impact this program has had on countless children and their families.

Research in this area changes lives, as I am sure research regarding vaccinations and dietary health has changed the lives of numerous others. The astounding results of research into this terrible disorder have changed the lives of many families, and as a result of this research, I am aware of families that have literally upended their lives to move across the country in search of programs like that of Dr. Lovass.

Mr. Chairman, there are some remarkable programs that have developed over the years with regard to autism, in particular some amazing advances in educating autistic children. But we still need more answers.

Mr. Chairman, again, let me thank you and the committee and the hard-working staff of the committee for holding this critically important hearing. For better or for worse, we must deal with this subject. This committee is taking a very important first step.

Thank you, Mr. Chairman.

Mr. BURTON. Thank you very much, Mrs. Chenoweth-Hage.

Mr. Kucinich.

Mr. KUCINICH. Thank you very much, Mr. Chairman.

I have to first inform you that I have a markup and votes in another committee, so I will not be able to stay. But I did want to come here specifically to support the cause of this hearing and your efforts in this regard.

While I agree with Mr. Waxman when he says the history of vaccinations has shown a lot of benefits, it is important for science to take note of the increased reporting with respect to rates of autism in recent years. If we have a higher incidence of autism, this is an appropriate subject for a congressional inquiry, and I think it is also appropriate for us to ask questions not only of the witnesses here today but of the industry producing these vaccines. I am particularly interested in what are their production protocols for the vaccines which our children receive; how are the vaccines being made; what is in the vaccines; are there any differences in how the vaccines were made years ago and how they are made today; are there any different products in there?

These are questions which could lend themselves to an understanding of why there is an increased rate today, and it seems to be different than what it was years ago.

So I think that when you see the heartfelt concern which is expressed here, the witnesses who are appearing and are scheduled to appear, and when you see that there are scientists who are willing to address the question of a causal link between autism and a vaccine, and when you have a scientist who is ready to say maybe there is not a causal link—the fact that this debate has begun here suggests an important moment in this Congress and in this country on the issue of autism. We need to find out if there is a link, and if there is a link, we need to go right back to the way the vaccine is made and what it is made of—because the problem may not be in our children; the problem may be in what our children are being given.

So I thank you very much for your diligence, Mr. Chairman, and for your commitment and for your quality of heart on issues of public health importance.

Mr. BURTON. Thank you, Mr. Kucinich, and I want to thank you for all the help you have given us on a whole host of issues relating to the health of the people of this country.

Mr. KUCINICH. I want to say I would not be on this committee if it were not for Mr. Waxman inviting me to be on this committee, and I am on it because of my deep respect for Mr. Waxman, whom I revere as not just our leader, but for me, he has been a personal hero. But I think I am on a committee with two of the best people in the House, so I am pretty fortunate.

Thanks.

Mr. BURTON. I hope everybody heard that. That was from the other side of the aisle. [Laughter.]

Mr. BURTON. Mr. Ose has said he does not have an opening statement.

Mr. Hutchinson, do you have an opening statement?

Mr. HUTCHINSON. No, Mr. Chairman.

Mr. BURTON. OK.

We will now proceed with our witnesses. As a practice, especially since we are talking about something as important as the various problems that have been occurring with you folks with autistic children, I would like to ask everybody to rise.

On our first panel, we have Mr. Kenneth Curtis, Mr. James Smythe, Ms. Shelley Reynolds, Ms. Jeana Smith, Mr. Scott Bono, and Dr. Wayne Dankner.

Would all of you raise your right hands, please?

[Witnesses sworn.]

Mr. BURTON. Please be seated.

Mr. Curtis, would you like to start? What I would like to ask, because we have 19 witnesses, and this is a very big hearing today, is if you could try to confine your remarks to 5 minutes. Some of the doctors who have technical expertise that they want to express will be allowed a little latitude, but if you could stick close to 5 minutes, we would really appreciate it.

Mr. Curtis, would you like to start?

STATEMENTS OF KENNETH CURTIS, CATONSVILLE, MD; JAMES SMYTHE, CARMEL, IN; SHELLEY REYNOLDS, BATON ROUGE, LA; JEANA SMITH, DENHAM SPRINGS, LA; SCOTT BONO, DURHAM, NC; AND DR. WAYNE M. DANKNER, SAN DIEGO, CA

Mr. CURTIS. Certainly. Mr. Chairman, all of you, first of all, thank you for this opportunity to speak on behalf of my son——

Mr. BURTON. Would you pull the mic a little closer? The mics do not pick up as well as we hope.

Mr. CURTIS. Sure. Leave it to the radio guy to mess up the microphone.

Thank you again for this opportunity to speak on behalf of my son, my family, and children with autism nationwide; but mostly I am speaking on behalf of my son, because this is really his story.

Autism does not announce itself in the delivery room. When our son Morgan Scott was born, he looked like a Sharpei dog—he was wrinkled from head to toe. Things were sort of storybook for us at that time. We had a girl and a boy, a mom and a dad, and life was kind of like a picnic. But the clouds were rolling in, as it were.

Slowly, little drops of doubt began to fall. We wondered about the way he liked to watch Disney videos over and over, or how he would spin around and make strange noises and look at things out of the corner of his eye; the way he liked to line up his toys. Drop after drop—we wondered, and we waited to see what would happen.

He did not talk, and most of the time, he did not even seem to hear us. So we worried some more, and we wondered, until all of these little drops were like a downpour—and of course, we had to take cover.

Our doctor suggested a hearing test, but his ears were fine. He just would not talk. We tried speech therapy, but he still would not talk. Even with all of these odd behaviors, my son was a happy enough kid. He was loving, affectionate, he was ticklish, stubborn—just like any kid—but he would not talk.

Finally, when Morgan was a little more than 2 years old, we had a word for it, and the word was more terrifying and confusing than any of the things we were dealing with at the time. Of course, the word was autism.

But what did that mean? Of course, we thought of "Rain Man," but we also thought of all the horrible stories you hear about kids who repeatedly bang their heads against the wall, or bite, scratch, and sit in a corner, rocking and hugging themselves. Is it possible that this could be our little boy? It did not seem real—but obviously, it was.

Morgan was diagnosed as "moderately autistic," a term I have always thought to be a bit like being "moderately pregnant." So we began to immerse ourselves in information. We were determined to learn everything possible about autism—and when I say "we," I really mean my wife Kimberly. You have never seen a woman on a mission until you have seen a mother determined to save her child. There is no match for a mother's love. She read, she researched, she investigated, while I tried to come to terms with the idea that I might never be able to shoot hoops with my son.

Before long, we had a plan. We opted for the one-to-one intensive ABA therapy program developed by Dr. Lovass at UCLA. We spent thousands of dollars, wrangled with the school system, hired lawyers, lived in my grandmother's house to save on rent, and we began teaching our son in-home.

For 5 years, Morgan had between 30 and 40 hours a week of one-on-one therapy. At age 4, my son had more college friends than most fraternity brothers. He learned to read a little, to spell a little, to use the toilet—and most importantly, he learned how to listen to people, and he even began to talk a little bit.

I am a radio guy—I talk for a living—and the irony of having a son who does not know how to communicate with words is not lost on me. I know there are things that my son wants to say to me, and as he gets older, I can look into his eyes and see the frustration and the confusion. There is a little boy inside of him somewhere, and it is as if he is lost.

This is really what it is like. It is like being in the mall with your child, and you look down and discover he is not there anymore—that sickening feeling you get in the pit of your stomach. Except that every once in a while, I catch a glimpse of the real boy—the way his eyes light up when you bring the Christmas tree home; the way he smiles when he jumps into the pool, or the way he sits perfectly still, enraptured, when he got to see the symphony. He loves music, he loves animals, he loves trains, books, swings, ice cream, and even his family, of course.

But he cannot tell me his favorite color, or how his day at school was, or what hurts when he falls off the swing set. He still has not figured out how to express or reveal himself. And he does not seem to understand why this is so important to us.

I want to know why my son is locked inside himself. Is there a genetic disposition? Is it environmental? Is it something in the water? Do pesticides cause it—preservatives; antibiotics; immunizations; Nutrasweet; the time he fell and hit his head? It sounds crazy, but these are the things we have all heard and thought about, and the truth is we have no idea why our son is autistic, and we have to accept that.

But we love our son so much that we can never give up hope that he will 1 day carry on a conversation with us or even just say, "Hi, Dad," when I come home from work.

Morgan is a truly beautiful person in his own right just as he is right now. I have never met anyone, and I doubt I ever will, who lives more in the moment than my son. He is affectionate, imaginative, and even humorous sometimes. And I have learned more from him than I have from any other single person in my entire life. He is autistic, and that is just the way he is.

But not everybody is as lucky as we are. Morgan is not aggressive or self-injurious like a lot of individuals with autism. He is 8 years old. I have had a lot of time to come to terms with this. Even so, the frustration of dealing with autism is nearly eclipsed by the frustration and the lack of concrete information about this disorder.

Autism used to be considered rare, the kind of thing you see in movies or read about in books, but it never actually happened to anyone you knew. In January of this year, the Autism Society of America estimated that autism had increased from 15 out of every 10,000 individuals to 1 in 500. And the repercussions of this increase are so far-reaching.

These children will need specialized education and appropriate care for the rest of their lives. Are we honestly ready for this? Are our schools equipped to handle this increase? This overwhelming surge in this disorder is not just going to affect individual families. This is going to impact our community and the entire world in which we live.

My son is a beautifully colored thread in the fabric of my family. But even so, 1 in every 500 families should not have to live with this disorder. And what if these numbers keep increasing?

So here I am today, wearing the only suit that I own, discussing my son before the legislative arm of the ruling body of the greatest Nation in the world. Believe me, testifying here today is one of the most important things I have ever done, and with all due respect to the tremendous body of work before each of you, I would like to think that it is a very important day for you as well.

Thank you.

Mr. BURTON. Thank you very much, Mr. Curtis.

Mr. Smythe.

[The prepared statement of Mr. Curtis follows:]

Testimony of Kenneth Curtis

Before the Government Reform Committee

April 6, 2000

Autism - Present Challenges, Future Needs - Why the Increased Rates?

Autism doesn't announce itself in the delivery room. When our son Morgan Scott was born, he looked like a sharpee dog. Wrinkled from head to toe with extra flesh. Imagine a pink, chubby Michelin Man. We had a boy! And things were sort of storybook then, a girl and a boy, a Mom and a Dad. Life was a picnic, but the clouds were rolling in. Slowly, little drops of doubt began to fall. The way he wanted to watch Disney videos all the time, how he would spin around looking at things out of the corner of his eye, the way he liked to line up his toys… Drop after drop. But we figured it was too early to worry. We waited to see what would happen. He wouldn't talk – and sometimes he didn't even seem to hear us. But we waited some more, and worried some more, until all the little drops were a downpour, and we knew we had to take cover.

The doctor suggested a hearing test, but his ears were fine. He just wouldn't talk. So we tried speech therapy; but he wouldn't talk. Even with the odd behaviors, Morgan was happy enough - loving, affectionate, ticklish, stubborn. Just like any kid. But he wouldn't talk. So we waited and worried and wondered, what could be wrong? Finally, when Morgan was a little more than two, we finally had a word for it. And the word was more terrifying and confusing than any of the things we were dealing with at the time…

Autism?! What did that mean? Of course, we thought of "Rain Man". But we also thought of all of those awful stories you hear about kids who repeatedly bang their heads against the wall – or bite and scratch and sit rocking in a corner. Could this really be Mo? Our happy, quiet little boy with the fondness for Mickey Mouse? It didn't seem real.

But it was, of course. Morgan was diagnosed as "moderately autistic"; (a term I've always thought was a bit like being "moderately pregnant") and we were left to wonder what to do next. As you might expect, we began to immerse ourselves in information. We were determined to learn everything possible about Autism. Well, when I say WE, I really mean my wife, Kimberly. There is no match for a Mother's love, and you have not seen a woman on a mission until you've seen a

mother determined to save her child. This was my wife. She gave up the very notion of a career to memorize every bit of minutia ever written on the subject of Autism. She read, researched, and investigated, while I tried to come to terms with the idea that I might never be able to shoot hoops with my son.
It seems like every few months or so, a new and different treatment for Autism pops up. There are volumes of theories, reports, and conjecture, and Kim took it upon herself to weed through it all, with me in tow. Before long, we had a plan. We opted for the one-to-one intensive ABA Therapy program developed by Dr. Lovaas at UCLA. We spent thousands of dollars, wrangled with the school system, hired lawyers, lived in my Grandmother's house to
save on rent, and began teaching our son in-home.

For five years, Morgan had between 30 and 40 hours a week of one-on-one therapy. At age 4, Morgan had more college friends than most fraternity brothers. He learned to read a little, to spell a little, to use the toilet, and – most importantly – he learned how to listen to people and finally began to understand some of what we said to him… and finally…..he began to talk.

I'm a radio-guy. I'm in the business of Communication, and the irony of having a son who doesn't know how to communicate with words, is not lost on me. I know there are things that my son wants to say to me. As he gets older, I can look into his eyes and see the frustration and the confusion. As his 3 year-old brother speaks paragraphs around the pacifier stuck firmly in his mouth, I know that Morgan wants to be heard. There's a real boy inside of him somewhere, but he's lost.

That's really what it's like; being in the mall with your child and looking down to discover he's gone. That sickening feeling in the pit of your stomach, that lump in your throat, wondering what's happened to your baby.
Some days, I feel like that all the time. Except - every once in a while - I catch a glimpse of the real boy. The way his eyes light up when I bring the Christmas Tree home. The smile on his face when he jumps into the pool or the way he sits perfectly still, enraptured, when we go to the symphony. He loves music, animals, birthday parties (anyone's), trains, books, swings, ice cream, and his family.

But he can't tell me his favorite color, or how his day at school was, or what hurts when he falls off the swing set. He can label objects and count and tell me what color something is…. But he still hasn't figured out how to express or reveal himself through language. He doesn't seem to understand why this is so important to us.

Why? Why is that? Why is my son locked inside of himself? And – more importantly – what can I do to set him free? These are the two big questions that rattle around in your head when you have an autistic child. Sadly, there are no answers, just more questions: Is there a genetic disposition? Is it environmental – something in the water? Do pesticides cause it? Preservatives? Antibiotics? Immunizations? NutraSweet? The time he fell and hit his head? These are all theories that we've heard and considered over the years. For now, though, it remains a bone fide medical mystery. We have no idea why our son is autistic… and - honestly – it really doesn't matter that much to me. I don't care about WHY as much as I care about HOW.

How can we treat this overwhelming blanket of isolation that covers our son? And, again, there are many theories to consider: Vitamin therapy, facilitated communication, restrictive diets, behavior modification, steroids, anti-depressants, ritalin, secretin, and even swimming with dolphins….

So, I suppose we've come to the next phase of our "grieving process", if you will: Acceptance. We love our son so much that we could never, ever give up the hope that he'll one-day carry on a conversation with us. Or even just say, "Hi Dad" when I come home from work. I suppose the difference is that, somewhere along the line, it's become more of a dream than a hope.

Morgan is a truly beautiful person in his own right, just as he is. I've never met anyone (and I doubt I ever will) who lives more *in the moment* than my son does. He has no concept of time; there is only the here and now for Mo. I defy you to find a person who gets more enjoyment from a playground swing than my son. He is affectionate, imaginative, and even humorous sometimes – and I've learned more from him than I have from any other single person in my life. He's autistic, and that's just the way he is.

But not everyone can be so lucky. Morgan isn't aggressive or self-injurous like some people with autism. Morgan is eight years old. We've had a lot of time to come to terms with this. Even so, the frustration of dealing with Autism is nearly eclipsed by the frustration at the lack of concrete information about this disorder.

Autism used to be considered a rare disorder, the kind of thing you see in movies or read about in books, but it never actually happened to anyone you knew. Lately, the diagnosis has become almost commonplace. In 1998, the Autism Society of America estimated that autism occurs in nearly 15 of every 10,000 individuals. In

January of this year, that estimate increased to 1 in 500, and we still have no greater understanding of this disorder.

This hearing is entitled, "The Challenges of Autism – Why the Increased Rates?" … And I wish I could tell you. In fact, if anyone who comes before you today can answer that question with any significant degree of accuracy (or even certainty), it would be a dream come true for me. It would seem to me that we couldn't know why the diagnoses of Autism are increasing until we know *what causes Autism*. Or even exactly what it is. But we don't…
More research must be done. This is imperative. We have to determine once-and-for-all the cause and origin of Autism. It needs to be researched, documented, and free of dispute. Then we can move toward a cure.

I've lived with my son's disability for eight years now. After all the reading and research and treatments, I'm still no closer to really understanding what's wrong with Morgan. For eight years, people have been asking me, "What exactly *is* Autism?". For once, I'd like to be able to give them an answer without shrugging my shoulders.

The irony, of course, is that it probably won't make any difference for Mo. He's autistic, and – barring the discovery of a magic pill that cures autism – he's probably going to be this way for the rest of his life. And that's OK. He's a pretty happy kid, all things considered. We're lucky enough to be able to provide him with a good life. All that aside, one in every 500 families shouldn't have to live with this disorder… and what if the numbers keep increasing?

The repercussions of this increase are far-reaching. These kids will need specialized education and appropriate care for the rest of their lives. Are we ready for this? Are our schools equipped to handle such an increase? This overwhelming surge in autism will not only affect individual families, but entire communities and the world in which we all live.

And so here I am, in the only suit that I own, standing before the legislative arm of the ruling body of the greatest nation in the world. For me, this small diatribe is one of the most important things I've ever done… and with all due respect to the tremendous body of work before you; I'd like to think it's important for each of you, as well.

Thank you.
Kenneth & Kimberly Curtis

Mr. SMYTHE. Thank you very much, Congressman Burton, Congressman Waxman, and other Members of Congress, for this opportunity to speak here for my son and for the tens of thousands of autistic children around this country and the millions of people who are affected by this, literally—parents, brothers and sisters, aunts and uncles, grandparents, and so on.

I will keep my remarks to 5 minutes, but I would like to make three points here, and I would like you to write these down.

The first is that living with these children can be hell. They can destroy your entire home. You cannot keep anything nice around. They will ruin your rugs. They will jump off the furniture. They will move the furniture around the room, push it over, break things, clear counters with one sweep of the arm. And they do all of these things with no malice whatsoever.

One cannot take them to friends' homes. One cannot stay overnight at friends' homes. When one is at a friend's or a relative's home, they will be worse there because it is a strange environment.

The second point is that no one to my knowledge is consistently measuring acquired autism. And Congressman Waxman, you mentioned that there is no causal connection between autism and vaccines.

Mr. WAXMAN. I did not say that.

Mr. SMYTHE. That there is no measurable causal connection.

Mr. WAXMAN. I said there is a theory, and that theory is still controversial.

Mr. SMYTHE. Is unproven. And I would suggest to you that we are now defining autism behaviorally; that certain activity, certain behaviors on the part of these children cause them to be classified as autistic, and then, most of the medical community gives up. And there is a difference between classical autism, a child who is born autistic, that one knows is autistic, and most doctors have been trained about autism because that is the way they were born, and they show up that way; and this late-onset autism that we are seeing, this acquired autism, if you will. There is a tremendous difference, and there may be many different medical causes. But because, in our language, we are not making that distinction, we are not able to follow medical cures or even medical causation. So that is an important distinction which I think needs to be made for all of us and by the NIH.

If you look at the insurance companies, if a child is labeled autistic, they will not cover it. It does not matter what the cause of that behavior is. If you look at the educational models, if you speak to the professionals in education, they do not have a distinction to my knowledge in the way that children who are acquired autistic are trained, compared with children who are classically autistic, how they are educated. The end result is that our educational models are not recognizing that some of these children may in fact just simply be sick; they may just simply be diseased. As a result, we are letting them down, and they are going through the educational system basically being warehoused, without any treatment, either medically or educationally.

From a financial standpoint, the stresses are huge. When one has an autistic child, suddenly, a whole new world of potential trauma has opened up, and there is very little known on this subject with regard to treatment.

We have followed a number of different treatment programs—auditory integration therapy, vision therapy, speech therapy, occupational therapy, and sensory integration therapy. We have participated in swimming and horseback riding, had CAT-scans, allergy testing, stool analysis and urine analysis, and all kinds of blood analysis. What we have noticed is that there is often kind of an uncaring attitude by the providers of many of these services, that "Maybe we will find out what is going on." But their house is not being destroyed. They do not have the motivation or the drive, it seems, to research this process. But it is very important to research.

Our school system is so overwhelmed that a recent Indianapolis Star article said that the State of Indiana has now changed the rules, so that a special education teacher can include anyone who has a college degree. What kind of special education is that? There is such a need out there, and the burdens are only going to become much greater.

The waiting list for Indiana's Medicaid waiver in order for a parent to get some financial assistance here is 3 years, and as I understand, it is growing—it has to grow—with the increase in the numbers of these children.

The ignorance in the insurance industry is phenomenal. I noticed that Secretary Shalala and the First Lady spoke about the use of ritalin in children, and I have heard that 10 to 20 percent of children are now on ritalin. Has it occurred to anyone that there may very well be and almost certainly is a causal connection that is related between ADD and this increase in autism; that they may be all part of one spectrum? I suggest that this needs to be looked at. But we have to make distinctions in language in order to do that.

Mr. BURTON. Mr. Smythe, if you could summarize, please, we would appreciate it. I know that you have a lot to cover, and we do appreciate your testimony.

Mr. SMYTHE. Thank you, Congressman.

The bottom line is that there are ways to measure how at least some of what is now showing up as autistic behavior, seems to be immune-related is affecting the brain differently from most of us, how it can be treated and then cured, and how the treatment itself can be seen to produce results in the return of blood flow to the brain.

I sincerely request that the members of this panel, the National Institute of Mental Health, and the Secretary of Health and Human Services look very carefully into this process and support the healing of these children—at least the subset which is probably responsible for this large increase.

Thank you very much.

Mr. BURTON. Thank you, Mr. Smythe. We appreciate you being here.

Ms. Reynolds.

[The prepared statement of Mr. Smythe follows:]

Testimony

By

James Smythe
Carmel, Indiana

Given To
Government Reform Committee
Hearing on
Autism – Present Challenges, Future Needs – Why the Increased Rates?

April 6, 2000

Thank you for the opportunity to speak for my son and the tens of thousands of children, and the hundreds of thousands, if not millions of parents, siblings and grandparents suffering from "autism." (See Exhibit 1, Yazbak study). To be brief, our problems are severe, and they are exacerbated by ignorance and resulting inability to help on the part of doctors, health insurance companies, and schools.

Consider the following circumstances in your home, with your child:

- Your child urinates or defecates somewhere on the floor every day. He does the same every night in his room, because he is up at least two to four hours between one and five AM every night. If you go to visit friend or relative overnight, his behavior will be even worse, because he is in a strange environment.
- If you don't know where he is, and what he is doing, you know that you may regret it. He likes to play in the toilet, leave the water running in the upstairs tub, and open the door and leave. He doesn't know about traffic.
- When your child is up at night, he moves the furniture in the room regularly, sometimes pushing an entire dresser through the drywall. He spends hours jumping from the highest places he can climb to onto the hardwood floor. He laughs or screams uncontrollably, as if drunk. Noone in the house can really sleep … night after night.
- Your child only eats a few things: carbohydrates and sugars. He carries the food all over your home, and crumbs are everywhere. When you take him to a restaurant, he runs to strangers plates and begins eating their french fries without any acknowledgement. Or he puts his hand in their drink to get some ice. He may do this at any time during your restaurant visit, while regularly crawling to the floor to eat someone else's food left there.
- He will not sit, but must jump from all of the furniture in your home for hours at a time. He will push any lamp, picture, book, papers or porcelain pieces on the floor

without thought, sometimes clearing an entire counter with one sweep of his arm. He is not angry, can't be disciplined, and doesn't seem to feel pain.
- He sometimes opens the car door while you are driving.

This happened to us for two years, and we are not unique among these families. In our experience, it is hard to find babysitters for a child like this. Only grandparents have the love to help out, and many families do not have these. Some families have two or three autistic children!

The result is that life, as the family knew it before the child, stops. Time and possibilities for children's activities, friendships, and vacations are transformed into doctor's visits, laboratory tests, behavioral and speech therapist sessions, IEP and school educational struggles. Insurance companies refuse to pay medical bills for treatment. Friendships end for lack of communication. Siblings lack the attention they deserve.

Financially, the costs can be devastating. In 1998, we spent over $30,000 on treatments, programs, medicine and tests for our son John. We couldn't afford this, and needed financial help. Many families don't have such help available to them. They are stuck in a poor neighborhood with this condition, and no place to go for help.

Treatment programs for our son have included Auditory Integration Therapy, Vision Therapy, Speech Therapy, Occupational Therapy, and Sensory Integration Therapy. We have participated in swimming and horseback riding, the Option Program, and picture exchange programs. Tests have included CAT scans, allergy testing, elemental hair analyses, antioxidant tests, urine profiles, stool analyses, and numerous blood analyses.

The uproar over Secretin should be a teaching lesson to everyone that parents are desperate for results. And many ignorant, uncaring, or outright fraudulent providers of "services" of different kinds are preying on us. Our son lost the few words he had after Auditory Integration Training. We saw doctors charging $1,000 and more for a dose of Secretin.

Our school system would not tell us what programs were available to us, and denied us options we found out should have been fully available until we hired an attorney in the second year of the process. Now we are struggling with the nibbling away of the fifteen hours per week that our son is supposed to be receiving. The provider is subtracting time to prepare materials, take notes, write down observations, and talk to us. Our son is lucky to get 12.5 hours per week, and usually that is spent sitting on a swing observing, or watching him watch the weather channel rather than interacting with him. He is supposed to get 1 hour of speech therapy per day minimally, and gets twenty minutes twice a week from the system that receives federal funds for his autism. But we have learned that our school system is overwhelmed with the increase in incidence of these kinds of children. According to a recent Indianapolis Star article, the State of Indiana is so desperate for Special Education teachers that they will allow anyone with a college degree to be one. What kind of special education is this?

The insurance companies will pay nothing for a child with autism. We found no company without this exclusion in their contracts. The waiting list for Indiana's Medicaid waiver, if you get on the list and they don't "lose" your spot in the meantime, is now three years. Because early intervention can be critical, the wait can be devastating to a child's ability to recover.

But we now have great hope. After years of reading books about autism, trying to understand why some children come out of the condition and some do not, we have learned that the term "autism", as used today, is a ***behavioral diagnosis*** and ***not a medical diagnosis*** because of its expanded definition to include so many children with different degrees of anti-social/behavioral conditions. (see Exhibit 2, Washington Post article). However, for most children, the behavior is caused by an underlying medical condition and these children can be treated. None of the insurance companies, school or program providers, or even physicians in Indiana with whom we met, including the pediatric immunologist at our local children's hospital, made this distinction. Ignorance is rampant.

Perhaps because it is not their lives that are altered each day, they are not compelled to interrupt their lives to learn. For example, the pediatric immunologist said he did not treat autism. We said, "we're not asking you to treat autism; we are asking you to find out if he has an immune system disorder." He refused to assist us because: 1) the tests are not traditionally run in cases like John's, and 2) he could not justify running them to an insurance company. When we offered to pay for the tests ourselves, he still refused to order them. He told us that if we wanted these done, we would have to go to California and see Dr. Goldberg. He had Dr. Goldberg's information from us prior to the appointment, but still refused the logic of the reasoning for running the tests.

My wife Denise and I followed the secretin story carefully, as well as Dr. William Shaw's work at Great Plains Laboratory. We called and interviewed the physician who spoke on the television program Dateline, spent significant time on the phone with Dr. Shaw, and read about the peptide work being done. We followed every thread we could find on the Internet, trying to understand all of the pieces of the puzzle and the conditions necessary for it to work, as Dr. Rimland and DAN (Defeat Autism Now) seemed to be promoting the use of Secretin for some children. During this time, I followed the web site of Dr. Sydney Baker, one of the DAN Protocol authors (see Exhibit 3), and found his conclusion ***"my present view is that autism and related developmental problems in children will turn out to be of viral origin"*** and his link to Dr. Goldberg's website, **neuroimmunedr.com**. (see Exhibit 4).

On Dr. Goldberg's site, I found, for the first time in two years, a cogent medical explanation backed with systems for diagnosis, treatment, and scientific measurements of progress toward healing for children tested to be immune deficient. (see Exhibit 5). The site is an oasis of understanding and treatment possibilities for children with autism, attention deficit disorder (ADD), and progressive developmental disorder (PDD) caused by neuroimmune disorders. It made sense to me that if there is viral or autoimmune cause to the illness, the treatment for such cause would be fundamental to a cure.

We learned, by having blood tests and immune panels prepared from our son John's blood tests (something no physician before had thought to do), that he had high HHV6 titers and low Natural Killer (NK) cells, a condition which is not caused genetically, but which is a disease probably brought on by genetic susceptibility. However, John is now curable!

Treatment began a year ago, and despite two setbacks due to illness in the process, John is improving very steadily. The life described in the beginning of this short presentation has dramatically changed, in too short a period to be attributed to maturity. We have a relationship with him. We all laugh and play together now. He always listens and sometimes follows simple directions. He doesn't mess the floor anymore. He has been sleeping through the night since December. His HHV6 titers are down. Dr. Goldberg expects John to mainstream in the next two years. With your help, it could be sooner.

John seemed to developed normally until about age twenty months. We thought he was the brightest of all of our children, and his brother, in eighth grade, just scored 1390 on the college SAT. The immunization schedules of John and his siblings show that John received the Hepatitis B vaccine the day he was born, May 11, 1995, and the third injection before he was age one. This was *before* his older siblings, who received theirs in 1996. (see Exhibit 6). In addition to this, Denise had gestational diabetes during her pregnancy with John, and he had a history of chronic ear infections beginning at two months of age. (see Exhibit 7). Perhaps, with Denise's diabetes, his pediatrician, a Carmel physician now specializing in the area of autism and ADD who, I am told, now treats over 400 children, should have been more prudent about the use of vaccines on the day he was born, and thereafter as his ear infections signaled a weak immune system. At some point, with all of the stress put on his immune system, perhaps because of the MMR/DPT vaccine or one of his many ear infections by age two, we believe that he suffered the equivalent of an immunological "stroke". We are now trying to recovery from this.

Families with autism need the following kinds of help to deal with this life-changing condition:

- Doctors educated to know that this behavioral condition may be caused by a treatable medical illness, and willing to learn new methods of diagnosis and treatment;
- Schools in which teachers and staff understand that many, if not all of these children are sick, not defective, and can be helped and rehabilitated to have a bright, normal future;
- Education for parents and the medical profession about the difference between the old, classic definition of autism and the new form of acquired autism;
- Insurance companies to recognize that these children are sick, but can and need to be made well;
- Money for research and education, to assist those qualified medical professionals who understand the problem to fill in the answers in the next two years and speed recovery of these children so that they resume normal development and become productive citizens.

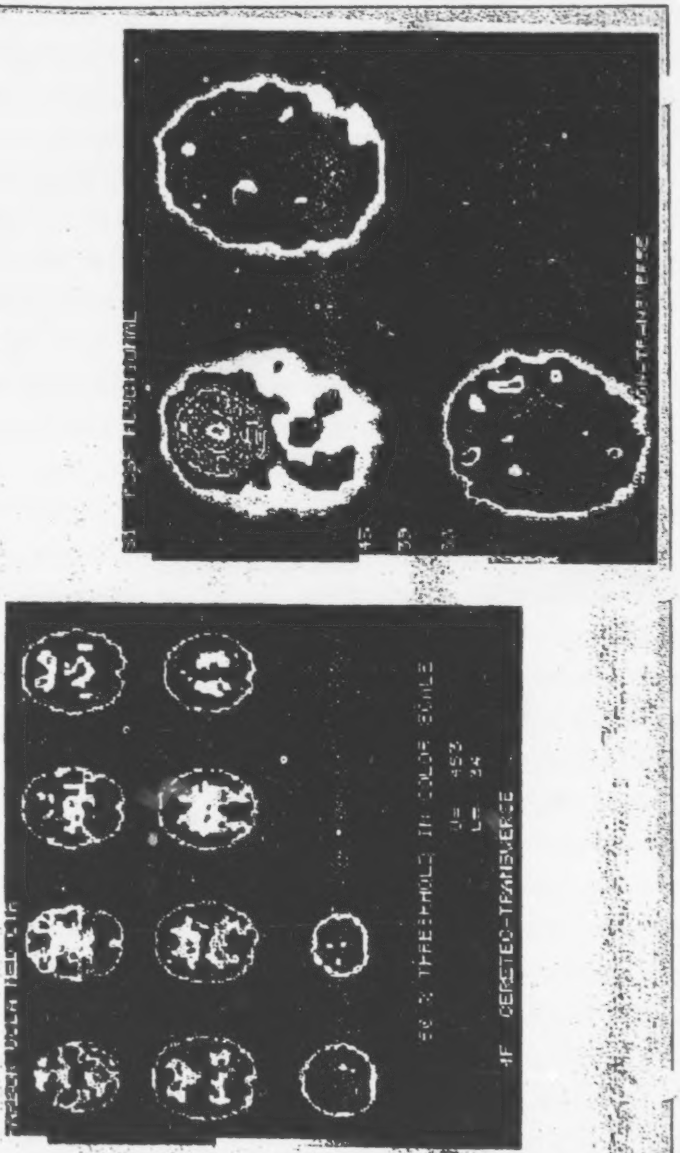
In May, 1999, 45 days into treatment for John, I attended a conference on Neuroimmune Dysfunction Syndrome at the National Institute of Mental Health. The curriculum vitae of most of the speakers, and a short summary of the presentations, is attached. (See Exhibit 8).

While I have great respect for the many physicians and professionals toiling to help these children, to my knowledge only the NIDS Medical Research Board combines the application of real science to make many autistic children well today with 1) predictable results, 2) scientifically measurable markers, and 3) commitment to the safety and well-being of the patients. They have a business plan and are confident in their ability to quickly speed their already predictable solutions for autism caused by neuroimmune dysfunction in a short time. (See Exhibit 9). We are only one of the many families seeing significant, predicted improvement. (See Exhibit 10). Independent medical research supports their scientific approach. (see Exhibit 11). Political affiliation among different autism camps will not affect the knowledge gaps needed to be filled for quicker neuroimmune solutions, but can delay the process necessary to attain it. Even if a genetic solution is attainable in ten years, we parents are willing to drive an earlier version of solutions today with our children. For the sake of our children and our families, please support the NIDS research team and the science that produces results now.

NeuroSPECT SCANS

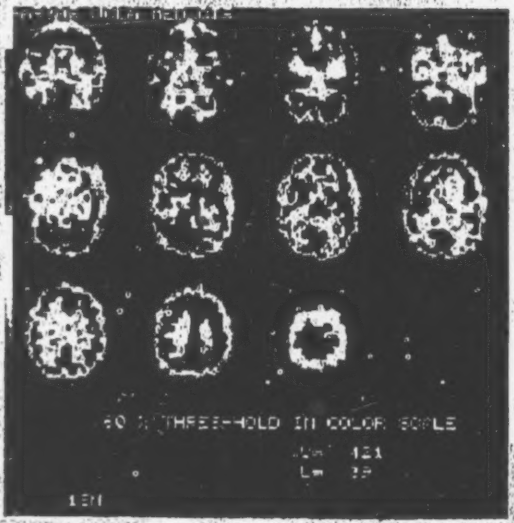
- Show *blood flow*
- Blood flow implies *function/activity*
- ***Key:***
  - ***Blue*** = Low / decreased flow / **poor function**
  - **Red** = **Good** / Normal function
  - Yellow / Green - Variable

4 yr. old female "Autistic"


50 % THRESHOLD IN COLOR SCALE

CFS / CFIDS - ADHD teenager:

18 yr. old male: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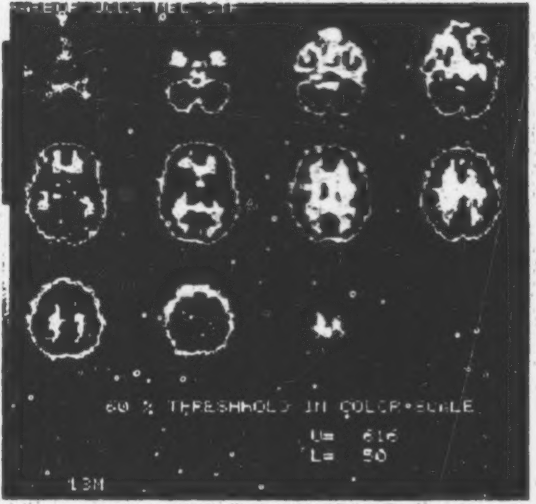
L= 39
18M

1 yr into Therapy: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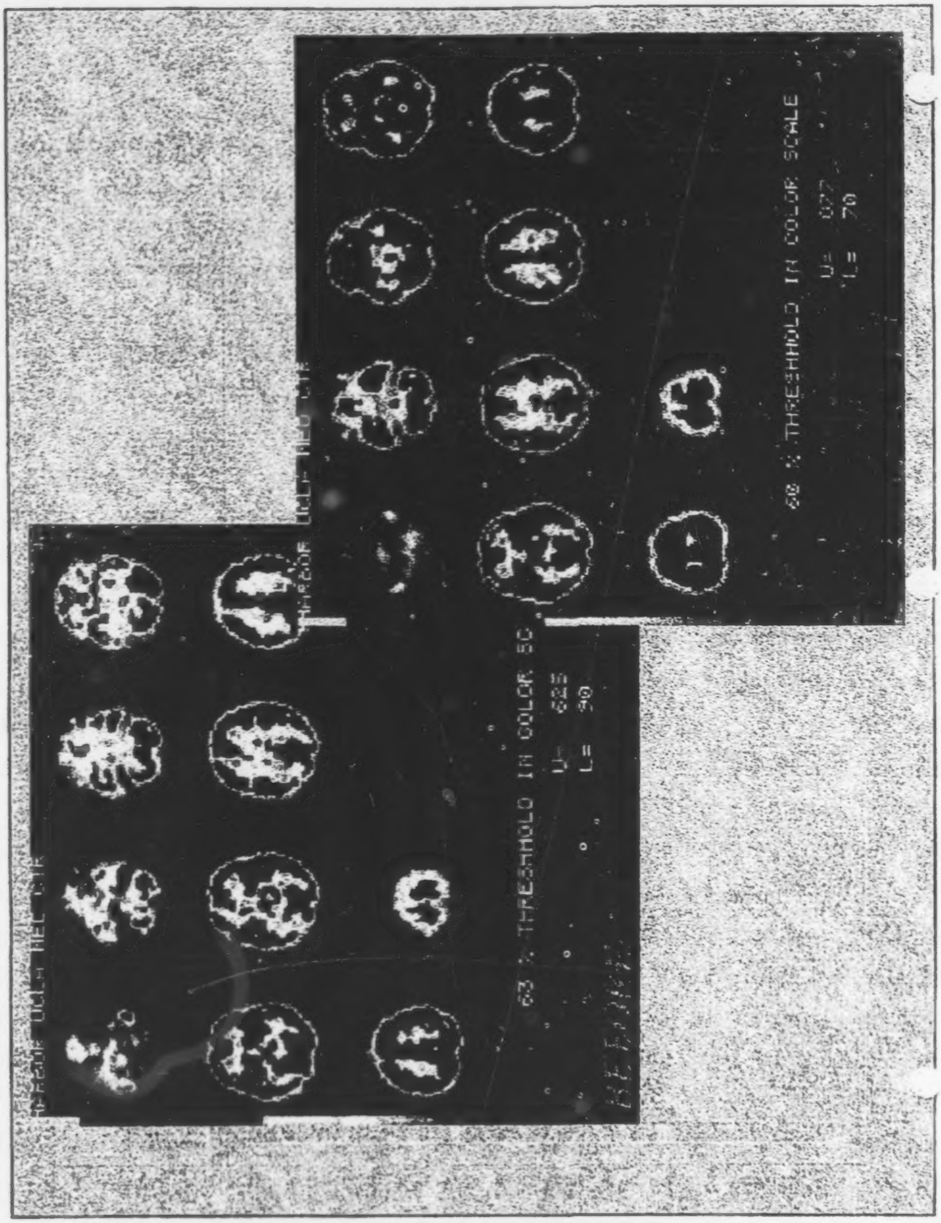
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L= 70
63 % THRESHHOLD IN COLOR SC
U= .025
L= 90

Ms. REYNOLDS. Mr. Chairman and Members, my name is Shelley Reynolds. I live in Baton Rouge, LA with Aidan, my husband of 8 years, and my children, Liam, who is 4, and Mairin, who is 2. I would like to thank you both for holding this hearing and allowing me to testify before you today.

I met Aidan in the 10th grade. We were in love with each other from day one. We dated all through college, and we got married as soon as we graduated. We had our own house, two cars, two careers, and two dogs. We were living the American dream.

Right after we were married, Hurricane Andrew, one of the most destructive hurricanes to ever hit the United States, slammed through Baton Rouge. Sustained winds of 100 miles an hour ripped off our roof, and 8 days without electricity left us with very little food or water. We promised each other we would never again be unprepared for such a disaster.

But 6 years later, hurricane-force winds blew into our home again. This time, the disaster was the diagnosis of autism for our first born son Liam. It completely tore our home apart, and the effects have lasted much longer than 8 days. No amount of preparedness can ready you for a storm such as this.

Liam was a normally developing baby until June 27, 1997, when he received his MMR and Hib vaccines. He did everything he was supposed to do. He cooed, rolled over, crept, crawled, pulled up and walked on time. He said "Mamma," he said "Daddy," he said "Love you." He learned how to sing "Itsy Bitsy Spider." He played finger games with us. He loved to interact, and he especially loved to show off for his grandparents.

We did all the well-baby checkups on time. I breast-fed him until he was 8 months old. I did not start solid foods until he was 4 months old. We did everything completely by the book.

But when he was 17 months old, shortly after he had received the shots, he started exhibiting some different behaviors. He was constantly taking off his shoes; he screamed if we dressed or undressed him; he would stare for hours in front of the television and would not move if you blocked the view. He could not tolerate playing in the sandbox anymore. He did not want to sing any of his favorite songs; he would cover his ears and scream "No."

We assumed he was just asserting his independence, since he was almost 2. And somewhere along the way, he developed chronic, nonspecific diarrhea, sometimes 8 to 10 times a day, and still suffers from that 3 years later.

By April 1998, I realized that Liam was no longer saying "Mamma" or "Daddy" or "Love you," so I took him for a speech and language evaluation. They told me that my 27-month-old child had the language capacity of an 8-month-old. This was a child who only months before would chime in "Ee-i-ee-i-o" at the appropriate moment when singing "Old MacDonald."

What had happened to our beautiful baby boy, and how could we help him? My husband and I decided to become advocates and work for increased funding for autism research and awareness. The answers may not come in time to help our son, but we are hopeful that we can persuade you to see the need for intensive research regarding this disorder which is affecting more and more children every year.

In Liam's case, we have no doubt that he developed his autism as a direct result of an adverse vaccine reaction. And personally, if I could strike the belief that my son's autism sprang from a routine childhood vaccination, that I held him down on the table for and had to go back to the Russian roulette of genetics, I would take it in a heartbeat, because the pain of knowing that I inadvertently caused him harm due to blind trust in the medical community, or a matter of inconvenience of yet another office visit taking time away from my job is nearly unbearable.

Many in the medical community continue to dismiss this as mere happenstance because autism often coincides with the time of vaccination, and state that there is no scientific evidence to back this up. My question to you is: How long does it take for a coincidence to surface time and time and time again, case after case after case, before it can become a viable hypothesis, especially when the solution to solving the problem seems so apparent? How can pharmaceutical companies concoct substances with mercury, formaldehyde, antifreeze, lead, aluminum, aborted fetal tissue and live viruses and not expect that as they continue to pour these highly toxic and reactive substances into children, increasing dose after dose, all on the same day, that it will not alter their minds and bodies?

Why would it be so completely impossible for a child to contract a chronic form of the disease rather than to have the "proper immunologic response," especially if their immune systems are not up to par? And where is their scientific evidence to back up the claim that this cannot happen, when it is published in the very package inserts, in their writing, that they have not studied the effects of these vaccines for more than a few weeks, or longer than the incubation of this disease itself?

What happens when you give multiple doses in 1 day or combine different diseases into one hypodermic needle?

I need someone to explain to me why it is acceptable to have products on the market that exposed my son to 37.5 micrograms of mercury in 1 day at a time when he should not have been exposed to more than .59 micrograms of mercury given his body weight. I should not be exposed to more than 5 micrograms, and I have 31 years of an immune history behind me. It is completely unacceptable. One size does not fit all when it comes to vaccines.

Through our organization, Unlocking Autism, we have talked with thousands and thousands of parents from across the country, and their story is the same: Child is normal; child gets vaccine; child disappears within days or weeks into the abyss of autism.

If you doubt me, I invite you to come to the "Hear Their Silence" rally on April 8th on the Mall, where the "Open Your Eyes" project will be displayed and view the thousands of pictures that we have called and realize that 47 percent of those people who participated believe that vaccines contributed in some way to the development of their child's autism.

Parents like me are relying on you to demand that the pharmaceutical companies retrace their steps once again and that the public health community look at the possibility that these things might indeed not just be a coincidence. They obviously have a forced market. They manufacture products that are required for every child in this country. We fear that it is possible that while seeking greater monetary profits, there may be some who have lost sight of the medical community's original goal regarding vaccinations—to protect children from harm.

I know my children, and I know what happened to my son. As far as I am concerned, the needle that silently slipped into my baby's leg that day became the shot heard around the world.

Thank you.

Mr. BURTON. Thank you, Ms. Reynolds.

Ms. Smith.

[The prepared statement of Ms. Reynolds follows:]

Testimony of Shelley Hendrix Reynolds

Before the Government Reform Committee

April 6, 2000

Autism – Present Challenges, Future Needs – Why the Increased Rates?

Mr. Chairman and members, my name is Shelley Reynolds. I reside in Baton Rouge, LA with my husband of eight years, Aidan, and my children, Liam, who is 4 and Mairin, who is 2. I would like to thank you for both holding this hearing and allowing me to testify before you today.

I met Aidan in the tenth grade. We were in love with each other from day one. We dated all through college and got married as soon as we graduated. We had our own house, two cars, two careers. We were living the American Dream. Right after we were married, Hurricane Andrew, one of the most destructive hurricanes to ever hit the United States, slammed through Baton Rouge. Sustained winds of 100 mph ripped up our roof. Eight days without electricity left us with very little food and water. We promised each other we would never again be unprepared for such a disaster.

But six years, later hurricane force winds blew into our home again, this time the disaster was the diagnosis of autism for our first born son, Liam. It completely tore our home apart. The effects have lasted much longer than eight days. And no amount of preparedness can ready you for a storm such as this.

Liam was a normally developing baby until June 27, 1997, when he received his MMR and Hib vaccines. Developmentally, everything was progressing completely normally. He cooed, rolled over, crept, crawled, pulled up and walked on time. He said all the things that parents crave to hear like "Momma", "Daddy" and "Love you." His expressive language increased to around 75 words. He was very social and had a completely infectious laugh. He liked music and learned the hand motions to little songs like "Itsy Bitsy Spider." He loved to interact and show off in front of his grandparents and our friends.

Well baby check-ups were kept on time. I breast-fed him until he was 8 months old. I didn't start solid foods until 4 months old. We did everything completely by the book and more.

When he was 17 months old, Liam started exhibiting some different behaviors. He was constantly taking off his shoes and screaming when we dressed and un-dressed him. He wouldn't let us brush his teeth anymore. He started staring into space when he watched a video on television and wouldn't move if you stood in front of the television. He couldn't tolerate playing in the sandbox anymore. He didn't want to sing favorite songs anymore and would just scream "No! No! No!"

We assumed he was just asserting his independence since he was almost 2.

Somewhere along the way he developed chronic, non-specific diarrhea ...sometimes 8 to 10 times a day.

A month before Liam turned two, visited my parents who live in Tennessee who had not seen Liam since the first week of July, 1997. They were shocked by the changes in him. My mother was alarmed at his lack of response when we tried to speak to him. She urged me to have his hearing tested. I had his hearing tested. It was normal.

By April of 1998 I realized Liam was no longer saying "Momma" or "Daddy" so I took him in for a speech and language evaluation. They told me that my 27 month old child had the language capacity of an 8 month old. This was a child that only months before would chime in "EIEIO" at the appropriate moment when singing "Old MacDonald."

We saw a pediatric neurologist, because that was on the list of things that you do with a suspected case of autism, and found that he had no seizure activity. His 12 hour EEG and MRI were normal. We continued doing blood work, stool and urine samples to determine his body chemistry, which was a complete disaster. His immune system was hardly operating. He had a host of bacterial, parasitic and fungal infections. The blood work also confirmed that he had suffered heavy metal exposure which had stippled his blood cells. Generally this type of the change in the blood is only seen when someone has been acutely exposed to a toxic metal. Liam had amounts of aluminum, mercury, tin, lead, and antimony that were off the charts. Liam was sick and in pain. We were scared and distraught. What had happened to our beautiful baby boy? How could we help him?

We decided to become advocates and work for increased funding for autism research and for awareness. The answers may not come in time to help our son, but we are hopeful that we can persuade you to see the need for intensive research regarding this disorder which affects more and more children every year. In California, only one of the 50 states, at least one child is diagnosed with autism every four hours, twenty-four hours a day, seven days a week. How many children have to slip through your fingers before you take notice that there is a serious problem here and that something other than genetics is causing it?

There are those who will argue that we are better at diagnosing autism today than in the past and that these children were once considered mentally retarded. However, according to a recent study, the mentally retarded have followed normal population increases and remained a steady constant while the autistic population has exploded. Is autism just the diagnosis du jour? Hardly. I would truly like to know where the parents of these autistic children were that did not recognize that their children were not talking, were spinning constantly in circles, doing odd things, abusing themselves, not making eye contact, having serious gastrointestinal disturbances, eating and sleeping problems, experiencing a failure to thrive due to malabsorption and suffering from excessive allergies. You cannot miss these children.

In Liam's case, we have no doubt that he developed his autism as the direct result of an adverse vaccine reaction. Personally, if I could strike the belief that my son's autism sprang from a routine childhood vaccination that I held him down on the table for, and had to go back to the Russian roulette of genetics, I would take it in a heartbeat. Because the pain knowing that I inadvertently caused him harm, due to a blind trust in the medical community or a matter of the inconvenience of yet another office visit is nearly unbearable.

Many in the medical community continue to dismiss this as a mere happenstance because autism often coincides with the time of vaccination and state that there is no scientific evidence to back this up. My question to you is, how long does it take for a coincidence to surface time and again, case after case after case before it can become a viable hypothesis, especially, when the solution to solving the problem seems so apparent? How can pharmaceutical companies concoct substances with mercury, formaldehyde, antifreeze, lead, aluminum and live viruses not expect that as they continue to pour these highly toxic and reactive substances into children, increasing dose after dose, all on the same day even, that it WON'T alter their developing minds and bodies? Why would it be so completely impossible for a child to actually contract a chronic form of the disease rather than have a "proper immunological response," especially when their immune systems may not be up to par? And where is THEIR scientific evidence to back up the claim that this cannot happen, when it is published in the very package inserts, in their writing, that they have not studied the effects of vaccines for more than a few weeks? Or longer than the incubation period of the disease itself? Or what happens when you give multiple doses in one day or combine different diseases into one hypodermic needle?

Could someone please explain to me why it is acceptable to have products on the market that exposed my child to 37.5 micrograms of mercury in one day when at that time he should not have been exposed to more than .59 micrograms of mercury given his body weight? Even a body as big as mine shouldn't be exposed to more than 5 micrograms of mercury in one day. That is completely unacceptable. One size does not fit all when it comes to vaccines.

Through our organization, Unlocking Autism, we have talked to thousands and thousands of parents from across the country and their story is the same. Child is normal, child gets a vaccine, child disappears within days or weeks into the abyss of autism. If you doubt me, I invite you to attend the Hear Their Silence Rally on April 8th on the mall where our Open Your Eyes project will be displayed. View the thousands of pictures we have collected and realize that 47% of those who participated believe that vaccines contributed to the development of their child's autism.

Parents like me are relying on you to demand that the pharmaceutical companies retrace their steps once again and that the public health community look at the possibility that these things might indeed not be just a coincidence. They obviously have no incentive to do so themselves. They are immune from liability and they have a forced market. They manufacture products that are required for every child in this country. We fear that it is possible that while seeking greater monetary profits there may be some who have lost sight of the medical community's original goal regarding vaccinations---to protect children from harm.

I know my children. I know what happened to my son. As far as I am concerned, the needle that silently slipped into my baby's leg that day became the shot heard round the world.

Ms. SMITH. Mr. Chairman and Members, I am Jeana Smith. I live in Denham Springs, LA with my husband Darrell and our four small children—5-year-old genetically identical twins, Jesse and Jacob, 3-year-old Garrett, and 16-month-old Julianna.

Darrell and I have always loved children, and we tried for over 6 years to have a child. We simply gave up on the idea that it was possible, and then I discovered I was pregnant with not one but two babies. I was completely overwhelmed.

Perhaps because I had tried so hard to have a child, I took especially good care of my body while I was pregnant with the twins. Our identical twins were born right on time and were completely healthy. We were absolutely thrilled. Our family was perfect.

One month later, we found dark blood mixed in with Jacob's diarrhea. Jacob had never had diarrhea before. We immediately took him to the doctor, who assured us that there was no problem. He mentioned that in the chaos that generally follows the birth of twins, we had been released from the hospital without them receiving their hepatitis B vaccine and wanted to give it to Jacob that day.

I questioned him, because it did not seem right to give a potentially ill child a vaccine, but he convinced me that it was routine and safe and not to worry.

Two months later, Jacob received his second hepatitis B vaccine and Jesse his first. On the same day, Jacob and Jesse both received their first DPT, polio, and Hib vaccination. From that day on, Jacob was constantly coming down with one ear, respiratory, or sinus infection after another. Jacob was constantly on antibiotics.

As his mother, I was heartbroken to see him sick or in pain practically all the time. As a new mom, I was embarrassed and frustrated to have a child who was always ill. I knew I was doing everything I could for him, and I could not understand why he was constantly ill.

Jacob met every developmental milestone that first year, right along with Jesse. They were two little peas in a pod and went everywhere together. At only 16 months of age, Jacob and Jesse received their first MMR vaccine. On this same day, they also received their fourth DPT, their fourth Hib, and their third hepatitis B. The following 24 hours, both twins slept most of the time, with over 100-degree temperatures, in spite of receiving the recommended Tylenol dosage every 6 hours. Immediately following that, Jacob began exhibiting strange behaviors. He was no longer excited or responsive when Daddy would come home from work. He began to become preoccupied with certain toys. He would spend long periods of time studying the way their wheels would spin or whether or not they were lined up just right. Any attempt to interrupt or distract him was met with great resistance and an eventual fit. During this time, Jesse continued to progress, starting to talk and interact with all the children around him.

Back to the doctor we went again, but this time with even bigger concerns about the growing developmental difference between Jesse and Jacob. And once again we were met with the "dominant twin" theory, that Jacob would probably be more quiet, Jacob would probably want to play by himself more often, and Jacob is fine, stop worrying.

Finally, we would not stand the undeniable difference between their language and communication skills. Something was most definitely wrong with Jacob. He could not express even the most simplest needs or wants. He could not ask for juice or something to eat. Jesse was chattering constantly. And at times, Jacob was so withdrawn that we could absolutely not reach him.

On days when Jacob is overloaded from sounds, colors, or lights, we cannot go anywhere. Autism not only isolates the individual whom it affects; it isolates the entire family. My husband and I have to go to the grocery store independently. When our other children have programs at school or birthday parties, one of us has to stay home, because Jacob cannot stand the outside stimulation. Our vacations have changed to only being able to go to the beach—no amusement parks, no baseball games, no family outings.

Unlike most parents of an autistic child, I do not have to wonder what Jacob would have been like. I know what he would have been like. I see what he would have been like every day in Jesse's eyes. I see Jesse excelling in school and in social activities. I see Jesse excited about T-ball; I know that Jacob will probably never play T-ball and that he cannot attend birthday parties.

For us, there is no denying that in Jacob's case of autism, the answer does not lie in genetics, but in a catalyst. The thousands of hours of research that we have spent searching and retracing his regression continue to point to the fact that the road of Jacob's autism began when his immune system was damaged by the hepatitis B vaccine he received when he was ill. The final blow was the adverse reaction to the host of vaccines he received 16 months later. We are certain that for Jacob, the catalyst was his vaccine.

I cannot bear the thought that after waiting so long and being so careful carrying my twins, I was so easily persuaded to immunize Jacob without knowing all that I should. I should have taken the time to find out what his risk of contracting hepatitis B at only 1 month old was. I did not do that. I should have found out about all the toxic metals that are used to manufacture the vaccines. I did not do that. I should have known back then what I do today. I did not. I trusted his pediatrician. I trusted the CDC. I was persuaded to believe that I was doing the best thing I could to protect my child.

No scientist, doctor, researcher or parent looking for answers or resources should never have to question where the funding will come from. It has to be here, and it has to be here now. I implore you to act now. Please—we do not have the time to wait for another hearing and another panel of parents and experts to advise us that this epidemic is waiting in the wings. We are swiftly and silently losing a generation of children to this disease that possibly could have been avoided. Please let this country be the leader in seeing the percentages of autism decrease and not increase.

Every night, Darrell and I tuck two beautiful little boys into bed. On the outside, they look the same. Their pajamas are the same; their bed covers are the same. Everything on them is the same. They have the same ears, and they have matching toes. As Darrell and I sit in between their beds, we talk to Jesse about his day. He gives us all the details of his day at school and tells us everything he did with his friends. He talks about how excited he is for the next birthday party that will come this weekend. He talks to Darrell about working on his batting swing to prepare for T-ball in the summer.

As he drifts off to sleep, we turn and look at Jacob. We know that even at only 5 years old, Jacob will never be able to enjoy the simple pleasures of childhood the way Jesse does. He will never be on a sports team. He cannot enjoy the fulfillment of a birthday party or friends. This difference is real. We know that Jacob's autism will not go away.

When they fall asleep, we once again see two beautiful, matching faces. We know what should have been. It is the only time that their faces match. Even though they are identical, Jacob's countenance left when he was 16 months old. The light behind his eyes was replaced with a blank, lost, bewildered stare.

Thank you.

Mr. BURTON. Thank you, Ms. Smith.

[The prepared statement of Ms. Smith follows:]

Testimony of Jeana Smith

Before the Government Reform Committee

April 6, 2000

Autism - Present Challenges, Future Needs - Why the Increased Rates?

Mr. Chairman and Members. I am Jeana Smith. I live in Denham Springs, LA with my husband Darrell and our four children... 5 year old genetically identical twins, Jesse and Jacob, Garrett who is 3 and our grand finale' Julianna, who is 16 months.

Darrell and I have always loved children. For six years we tried, unsuccessfully, to have a child and decided that it simply wasn't meant to be. To our complete surprise I found out that I was pregnant with twins - a double blessing!

Perhaps, because we had tried so hard to have a child, I took especially good care of my body while I was pregnant with the twins. Our identical twins were born right on time and completely healthy. We were absolutely thrilled. Our family was perfect.

One month later we found dark blood mixed in Jacob's diarrhea. Jacob had never had diarrhea before. We immediately took him to the doctor who assured us the blood was from a rectal tear. He mentioned that in the chaos that generally follows the birth of a baby, much less twins, we had been released from the hospital without vaccinating the twins with Hepatitis B. He wanted to vaccinate Jacob right then. We questioned him because it did not seem right to give a potentially ill child a vaccine, but he convinced us that it was routine and safe. Not to worry.

Two months later, Jacob received his second Hepatitis B vaccine and Jesse his first. On this same day Jacob and Jesse both received their first DTP, Polio and Hib vaccination. From that day, Jacob was constantly coming down with one ear, respiratory or sinus infection after another. Jacob was constantly on antibiotics. As his mother, I was heartbroken to see him sick or in pain practically all the time. As a new mom, it was embarrassing and frustrating to have a child that was always ill. I knew I was doing everything I could for him, and couldn't understand why he continually ill.

Concerned, we asked our pediatrician and he explained that Jesse was the dominate twin, and this was perfectly normal for Jacob, slightly smaller, to have a weaker immune system and to be prone to common infections.

Jacob met every developmental milestone that first year right along with Jesse. They were two peas in a pod and did everything together.

At only 16 months of age Jacob and Jesse received their first MMR vaccine, along with their fourth DPT, fourth Hib, and their third Hepatitis B. The following 24 hours both twins slept most of the time with 100 degree temperatures, in spite of receiving the recommended dosage of Tylenol every six hours. Just days later, Jacob began exhibiting strange behaviors. He was no longer excited or responsive when Daddy came home from work. He became preoccupied with certain toys. He would spend long periods of time studying the way their wheels would spin or whether or not they were lined up just right. Any attempt to interrupt or distract him was met with great resistance and an eventual fit. During this time, Jesse went along with business as usual.

Back to the doctor we went again, this time with very serious concerns about the growing developmental difference between Jesse and Jacob. And once again, we were met with the dominate twin theory. Jacob would probably be more quiet. Jacob would probably want to play by himself more often. "Jacob is fine, stop worrying."

Finally we could not stand the undeniable difference in their language and communication skills. Something was most definitely wrong with Jacob. He could not express even his most simple needs or wants. He couldn't ask for juice or something to eat. Jesse was chattering constantly. And at times, Jacob was so withdrawn that we absolutely could not reach him.

In a waiting room, in front of several other parents, we received Jacob's first official diagnosis. The Director of LSU's Speech and Hearing clinic callously and simply stated, "Mrs. Smith, Jacob is autistic. There is nothing that we can do for him today. You will need to call back and make an appointment to see one of our speech therapists." I will never forget the day I heard those devastating words, the ones I knew were coming, but words I would not allow my heart to tell my head. I walked out of the office with Jacob in my arms, sobbing and bewildered. THIS IS COMPLETELY IMPOSSIBLE my mind screamed. Autism is genetic and Jesse is fine. What is going on with my baby?

Because we were facing the overwhelming news that our perfect-looking son had a serious life-long disability, the word of one "expert" was simply not good enough. We continued seeking answers. Three more diagnosis' quickly followed.

Jacob is a beautiful child who has abnormal sleep patterns and has lived with continuous physical pain. His lack of sleep keeps me up all hours of the night, and by the time I finally fall asleep, it is time to wake the kids up for school and start the day. We are constantly working with Jacob to help him understand the outside world so that we can maybe go to the grocery store, the mall, the gas station or McDonald's without him getting hysterical from sensory overload from all the fluorescent lights and sounds.

What may sound like water dripping to us may sound like a massive water fall to an autistic child. What may sound like squealing tires to us may sound like the Indy 500 up close to a child like my son. On days that he is "overloaded" from sound, colors or lights, we can't go anywhere. Autism does not only isolate the child that it affects. We can't take the family out to dinner or out to have fun. When the other children may be waiting in anticipation to go have a day out with mom and dad, one of us will have to stay home with Jacob because he is so agitated. If one child has a school program and Jacob is frustrated, then we have to see that crestfallen look on the child's face because both mommy and daddy cannot go, since one has to stay with their brother. We know if we take him in public, there will be a scene. Little things such as this "rob" life's enjoyment from our other children.

Unlike most parents of autistic children, I don't have to wonder what my child would have been like. I see what he would have been through Jesse every day of my life. I see Jesse excelling in school, and his social activities. He will be starting a tee ball team this summer. I will have to find a babysitter to watch Jacob so that our family can attend Jesse's games.

This may not seem like a lot to some people, but not being able to do things together is not fair to the other children in the family. We have had to explain to Jesse and Garrett what Autism is. That is not an easy concept for two small children to understand. And it is not easy knowing that someday when my husband and I are gone that one of our children may have to take care of Jacob for the rest of his life. We should not have to prepare our children for that possibility. But we have to think ahead. What happens if Darrell and I go somewhere together and something happens to us? Who will take care of Jacob and see to his needs? Who will understand what he is going through? Who will defend Jacob when we are not there to do it and he cannot do it for himself? Who will understand his frustration if we someday aren't around? These are things that keep us, as parents, awake at night worrying.

For us, there is no denying that in Jacob's case of autism, the answer does not lie in genetics but in a catalyst. The thousands of hours of research that we have spent searching and retracing his regression continue to point to the fact that the road to Jacob's autism began when his immune system was damaged by the Hepatitis B vaccine he received when he was ill. The final blow was the adverse reaction to the host of vaccines he received by 16 months. We are certain that for Jacob, the catalyst was his vaccines.

With Jacob's initial diagnosis, many doctors and professionals suggested that we put him on medications designed to mask autistic behaviors. WHAT AN OUTRAGE! To give our small child drugs to cover up what was actually happening inside his body did not make sense. We wanted to find out what his body was doing and treat that first.

We were blessed with a wonderful Doctor in Louisiana, Dr. Stephanie Cave. She ran blood and urine tests to find out what amino acid, vitamin and mineral deficiencies and immune system dysfunctions Jacob had, along with his exposure to heavy metals, invasive fungal infections and extensive food allergies. The results were shocking. It was amazing this little guy was able to do as well as he did.

After placing Jacob on a structured, nutritious diet, supplementing his deficiencies and working to restore his immune system, Jacob is giving perfect eye contact and beginning to initiate and interact in conversation. He has made incredible strides. Jacob is still autistic. There is no doubt about that. But he is only five. The progress we have seen inspires us to shout from a mountaintop the hope available to so many children! For him, it is evident that autism is not always a traditional congenital genetic disorder. It can be an acquired syndrome. And that is why I am here today.

There is a huge epidemic of autism in this country with countless parents that believe, as I do, that their child's autism is the result of a vaccine reaction. I have talked to thousands of parents and they know their children! They are not looking for a scapegoat. They are looking for answers and truth. They tirelessly look at every possible reason their perfectly normal child could slip away so quickly. If parents were looking for an excuse for why their child could be snatched away so quickly, they certainly would not choose to put the blame on something they did to protect their child and keep them from harm.

I can't bear the thought that, after waiting so long and being so careful carrying my twins I was so easily persuaded to immunize Jacob without knowing all I should have. I should have taken the time to find out his risk of contracting HepB, I didn't. I should have found out about all the toxic metals that are used to manufacture the vaccines. I didn't. I should have known back then what I do now. I didn't. I trusted his pediatrician, I trusted the CDC. I was persuaded to believe I was doing the best thing I could do to protect my child.

I can assure you that this epidemic will not go away until we address it. Every scientist, doctor, researcher, parent looking for answers and resources should never have to question where their funding will come from. It has to be here now! If you don't deal with this today, how will you deal with it in 15 years?

Three years ago when Jacob was diagnosed, autism affected at least 1 in 500 children. Now it affects one in 300 children nationwide. In some places it affects as many as 1/127. Today, Coast to Coast the school and service systems are over run. In California alone the tax dollars will cost 2 million dollars per child diagnosed with autism. Last year alone almost 2,000 children were diagnosed with autism and added to the already .... system. We cannot run from this. The numbers are rising. The numbers are real. Autism and the children, and adults and families affected by it are living in the towns and cities of every person in this room.

I implore you to act now. You do NOT have time to wait another year for another hearing and another panel of parents and experts to advise you that an epidemic is waiting in the wings. We are swiftly and silently losing a generation of children to a disease that could possibly be avoided. While we are taking our children every afternoon to the therapies that they need to make it through the day, or charting the 15 supplements that we have to give them in order to keep their body chemistry afloat, or monitoring every crumb or drop that enters their mouth in the hopes that it does not contain a trace of gluten or casein, or educating the teachers that work with our children everyday, or fighting the school system to make sure that our children get the education that they are entitled to, or arguing with the insurance company about the fact that yes that very expensive test was absolutely necessary in determining the best course of medical intervention for my child, or working two jobs to pay for the multitude of services that our children need because the government can't keep up with the demand, we need YOU on the front lines demanding answers from the medical community. We need YOU on the front line requiring the pharmaceutical companies to come up with the research that they should have done decades ago. We need YOU to fund the independent scientists so that they can maintain their objectivity in investigating the possibility of a connection between vaccines and autism. We need YOU to help fund the research that will ultimately lead us to a cure for these kids.

Please, let this country be the leader in seeing the percentage decrease not increase.

Just like Jacob, these children are not without hope. They can get better. Jacob is doing better than we ever imagined. But we have fought, and scratched, and struggled to get him the things that he needs. A child with Autism is a puzzle for us all. And each piece of the puzzle is incredibly important. But closing your eyes and relying on 40 years of medical rhetoric that has dismissed autism as a mere genetic, psychiatric disorder will keep parents like me from having the answers that we certainly deserve. Good science research into the autism/vaccine connection must begin NOW in a serious and accelerated way, with independent research institutes like the M.I.N.D. Institute at U.C. Davis leading the way.

Every night Darrell and I tuck two beautiful little boys into bed. On the outside they look just the same. Their bed covers and pajamas match, their cheeks and hair match, There is nothing on their body that does not match, even their toes are the same. As Darrell and I sit in between their beds we talk with Jesse about his day. He gives us all the details of his day at school and tells everything he did with his friends. He talks about how excited he is for the birthday party at his cousins house this weekend. He talks with Darrell about working on his batting swing to prepare for T ball this summer. As he drifts off to sleep, we turn to tuck in Jacob. We know, even at only 5, Jacob will never be able to enjoy the simple pleasures of childhood the way Jesse does. He will never be on a sports team. He cannot enjoy the fulfillment of birthday parties or friends. The difference is real! We know Jacob's autism will not go away! When they fall asleep, we once again can see two beautiful matching faces and know what should have been. It is the only time their faces match. Even though they are identical, Jacob's countenance left when he was 16 months old. The light behind his eyes was replaced with a blank, lost, bewildered stare.

I cannot count the times Darrell and I have cried quietly in between their beds while they sleep. We cannot imagine that anyone else could understand such grief. Tomorrow morning, or perhaps, in the middle of the night we will be awakened by the reality of their difference, by the reality that Jacob is autistic.

Mr. BONO. Before I begin, I would like to give you the perspective of an autistic parent.

Right now, I am more nervous about where my son is, because I do not see him, than I am about being before you today. That is a constant worry in the mind of a parent of an autistic child.

My name is Scott Bono, and I live in Durham, NC with my wife Laura and my children, Dylan, Ashley, and Jackson. I have read the testimony and heard the stories of other parents in similar circumstances—change that to "identical circumstances." Our story is not much different.

We had a perfectly normal pregnancy and birth of our son. In the first 16 months of life, he learned language, played with toys, appropriately began pretending skills, initiated contact with his twin sisters, and could light up a room with his wonderful personality. He was brighter than most, and he could even tell the difference between a Concord jet and a 727 at such an early age.

On August 9, 1990, Jackson would begin a journey into silence, bewilderment, and a medical enigma. That was the day he received his MMR immunization. He would not sleep that night. In the days to follow, he would develop unexplained rashes and horrible constipation and diarrhea. After eating, he would experience projectile vomiting that would scare him.

His normally very healthy body was being ravaged by an invader. Over the next weeks, he would slip away, unable to listen or speak. He retreated into what we now know as autism. He became allergic to everything in his world. His immune markers skyrocketed.

What was the reason for this change? It is my sincerest believe that it was that shot.

The single biggest challenge in raising an autistic child is getting appropriate, informed, and competent medical services. As I sit before you today, autism is, as it has been for decades, viewed as a psychological disorder. I cannot help but wonder about and get frustrated by the lack of medical and physiological intervention for all of these children.

I live just 3 miles from Duke University Medical Center, yet for one of the most effective treatments for Jackson's gastrointestinal problems, I drive 12 hours for a procedure that takes 5 minutes. I have been doing this for the past 2½ years and will be making this trip 13 times this year alone.

To dismiss Jackson's acidic diarrhea for 7 years because "autistic children sometimes do that" is just what happened. That is just unacceptable. As my son's advocate, I know that he is not receiving the medical treatment he needs, and I believe that as long as autism is regarded as a psychological disorder, this will always be the case. We need and seek responsible, effective and caring physicians who do not dismiss the patient's ailments as "behaviors," but look at them as treatable medical conditions with appropriate medical intervention.

This is what I believe to be the single biggest problem in getting group insurers to pay for medical services. Insurers must pay according to their contract. It is the law. But if a doctor says the visit to his office is for the treatment of autism when the autistic child is being seen for gastrointestinal distress, the insurer will not pay

89

the claim. If, however, the diagnostic code for the visit shows that it is for gastrointestinal distress, the bill will be paid. The diagnosis of autism is used as a shield by some insurers to deflect the responsibility of paying for medical and remedial treatment for these children's medical problems.

The expenses of seeing Jackson's needs are overwhelming—hundreds of thousands of dollars over the past 8 years. After going through all of our savings and retirement, we continue to accumulate debt to meet his educational and therapeutic needs and his medical needs.

Our priority right now is to get him well. There are other costs besides financial. Jackson is on a very strict diet that takes time and money. If he eats offending foods, he gets a rash, has diarrhea, and we will not sleep for the next 5 nights. His behaviors will worsen.

How do I put a cost on not sleeping for 6 years? How do I put a cost on attention not paid to my daughters because I am seeing to the needs of my son? How do I put a cost on locking every door and window at all times for fear of him wandering out of the house?

Financial burden is only part of it. It is only part of the picture that families with autistic children face. If the price of eradicating measles, mumps, rubella, or any other illness is thousands of autistic children or health-impaired children, is it worth it? Have we simply traded acute illness for chronic disease? Is that worth the price?

Autism has reached epidemic proportions, and the numbers are still growing. We must allocate funds to find the cause and the cure. The U.S. Department of Education indicates the increase in autism is 900 percent in the 8 years since 1992. If tooth decay went up 900 percent, we would be scrambling for answers.

The statistics can no longer be ignored. Thousands of parents who claim their children were developing normally until the MMR vaccine should no longer be ignored. We all cannot be wrong.

As elected officials, you hold the public trust, the essence of faith in Government. Your challenge is to uphold that trust.

Thank you.

Mr. BURTON. Thank you very much, Mr. Bono.

Dr. Dankner.

[The prepared statement of Mr. Bono follows:]

April 6, 2000 – "The Challenges of Autism – Why the Increased Rates?" – Scott Bono

Thank you, each of you, for allowing me to come before you today. I will talk about the challenges of raising an autistic child, with particular attention given to finding treatment options, the personal financial burden of treatment, and insurance reimbursement issues.

I have read the testimony and stories of other parents in similar circumstances. Our story is not much different. We had a perfectly normal pregnancy and birth of our son. His first sixteen months of life were filled with joy. He learned language, played with toys, appropriately began pretending skills, initiated contact with his twin sisters, and could light up a room with his wonderful little personality. He was brighter than most and could even tell the difference between a Concorde jet and a regular one at such a young age. He was a joy.

On August 9th, 1990, Jackson would begin a journey into silence, bewilderment, and a medical enigma. That was the day he received his MMR immunization. He would not sleep that night. In the days after the vaccine, he would develop unexplained rashes and horrible constipation and diarrhea. After eating he would experience projectile vomiting that would scare him. His normally very healthy body was being ravaged by an invader. Over the next weeks, he would slip away. Unable to listen or speak, he retreated into what we now know as autism. He became allergic to everything in his world. His immune markers skyrocketed. What was the reason for this change? It is my sincerest belief, that what caused his autism was that shot.

We would visit our pediatrician many times over the next few months for help, only to be dismissed. "There is nothing to worry about, boys develop slower than girls, you are comparing him to your daughters."

The single biggest challenge in raising an autistic child is getting appropriate, informed and competent medical services. As I sit before you now, autism is, as it has been for decades, treated as a physiological disorder. I can't help but wonder about and get frustrated by the lack of medical and physiological intervention for all of these children. Unfortunately, there are more autistic children today. Fortunately, there are more informed parents—who thanks to the internet have more access to information than no other time are able to affect changes in their children. They are not accepting the line, "there is not much information and research about your child's condition," and they have pulled a small group within the medical community into thinking out of the box..

The parents are the ones who have been finding treatment options for their children. They have to beg, coax, and cajole to get the doctor to think that the treatment they believe will help their child, was the doctors idea before the treatment is made available for their child. And, therein lies the problem. Doctors don't know what treatment options are available.

Treatments are available. But, so few doctors are really willing to work with these children. If you can find a doctor who is willing, you will wait months for the opportunity to see them. If you find that special doctor who is willing to work with these children, they become swamped with new patients; until they can't or won't accept any new patients.

I live just three miles from Duke University Medical Center, yet for one of the most effective treatments for Jackson's gastrointestinal problems, I must drive 12 hours every four weeks for a procedure that takes less than 5 minutes. I have been doing this for the past two years, and will make this trip 13 times this year alone.

In medical school, autism is not taught as a medical disorder. If it is mentioned, it is something that a psychologist would delve into, not a medical student.

As long as autism is explained by, and treatment options exclusively available from psychologists finding the cure will be out of reach.

A psychological explanation of behavior does nothing for explaining a medical or physiological situation. Here is an example:

You have three bran muffins and a glass of prune juice for breakfast. You hop on the metro to get to your Capitol Hill office, and you expect to be there in 20 minutes. But, the train in front of yours has stopped, and you are stuck for the next 90 minutes. Paralyzed by the fear of the normal demands of your body, you begin to sweat. You become more irritable. The last thing you want to do is make small talk with people who suddenly recognize you. They think your abrupt behavior is weird. They wonder what you are "hiding" because no one else is sweating. You get the picture...

To explain your state of emotions does not help you. To develop "coping methods" and "strategies" is not what you need. You don't want a psychologist asking you if you are sure that there is not some "other reason" you are behaving in a perturbed and anxious manner. Your behavior is obviously emanating from a physical need. Autistic children are no different.

To dismiss my child's acidic diarrhea for seven years because "autistic children sometimes do that" is just what happened to Jackson. His diarrhea would be so acidic that if not immediately washed off would create blisters on his buttocks and legs. These episodes would happen at least 10 times a day. This is unacceptable.

As my son's advocate, I know that he is not receiving the medical treatment he needs. And I believe that as long as autism is regarded as a psychological disorder this will always be the case. We need, and seek, responsible, effective and caring physicians who don't dismiss the patient's ailments as "behaviors" but look at them as treatable medical conditions with appropriate medical intervention.

This is, what I believe to be the single biggest problem in getting group insurers to pay for medical services. Insurers must pay according to their contract. It is the law. But, if a doctor says that the visit to the office is for the treatment of autism, when the autistic child is actually being seen for gastrointestinal distress, the insurer will not pay the claim. If however, the diagnostic code for the visit showed that it was for gastrointestinal distress, the bill would have been paid. The diagnosis of autism is a shield used by some insurers to deflect the responsibility of paying for medical and remedial treatment for these children's MEDICAL problems.

I would like to recognize my son's doctor, as being the most caring, most willing to listen and help—Dr. Richard Layton. My wife and I truly love him for what he has done for our son and other children.

Today, you will hear, or have heard from, Dr. Andrew Wakefield. He too is a rare doctor. He is seeking to correct the gastrointestinal problems of his autistic patients. In doing so, he is challenging the "traditional" medical perspective on autism. What he does for me, as a parent, is give me hope that his work will spur on more treatment options, options that are already out there, but not thought of to help those with autism. He dares to question public health policy with respect to immunizations safety. Thank you Dr. Wakefield.

When Jackson's condition was at its worst, we were told by professionals/specialists that "he probably won't make it past age five or six" and that "institutionalization" is an option. Neither of which were alternatives for our family. My wife and I developed a plan that guided our efforts. Medical, educational and therapeutic were the major categories. The expenses for seeing to Jackson's needs are overwhelming—hundreds of thousands of dollars over the past eight years. After going through all of our savings, and our retirement we continue to accumulate debt as we try to meet his medical needs. Our priority right now is to make him well again.

Money is the means to measure financial costs. And I am but just one father of one family. How much are all of the families spending? What will the cost be to the taxpayers to educate these children? Some experts put that cost at $2 million per child until their 18th birthday.

There are other costs. To get a cup of coffee in my home, I have to unlock a padlock to get the sugar. Why a lock? Because if Jackson eats sugar, (or any thing else in that cabinet—wheat cereal for my daughters, flour, pancake mix, or certain fruits) he gets a rash on his bottom that is so bad he can hardly sit. No one sleeps for three to five nights and Jackson experiences massive diarrhea. Yet, these are the foods he craves. Why?

How do I put a cost on six years of not sleeping through the night? What is the price?

How do I put a cost of attention NOT paid to my daughters because I am seeing to the needs of my son?

How do I put a cost on locking every door and window at all times for fear of him wandering out of the house?

Dr. **DANKNER**. Honored committee members, fellow panel participants and members of the audience, I feel privileged today to appear before this committee to share my perspectives on autism, foremost as a parent but also from the additional perspectives as a pediatric infectious disease specialist and a scientist engaged in clinical research and evidence-based medicine.

My daughter Natalie, who is over there, is now nearly 13 years old, has autism, and has taught my family and me a lot about ourselves and how the world around us deals with individuals who appear different from the norm. She has been both a joy and a real challenge to live with, and we continue to live through these experiences every day, and I want to emphasize that.

We have weathered this storm by rejoicing in her triumphs and finding humor in past events, even when those events may have seemed unbearable at that time. And I should add that my wife, unfortunately, is the one who has to bear most of these unpleasant experiences.

We have found that our daughter's greatest needs have been in the area of education and for a highly structured environment to allow her some control over the events of her life. It is in the area of education that we have experienced our greatest challenge and have been labeled by our local school district administrators as the most difficult parents they have had to deal with. In the context of that meeting, we found this statement an insult, and there were other personal comments made to my wife that essentially have put her in a position where she will not talk to the school district administrators any longer.

But we have been convinced by our friends and family that we should wear this as a badge of honor. If anything, it highlights the advocacy that we have championed for our daughter's right to an appropriate education that addresses her individual needs and the manner in which she learns best. I should point out that probably every parent on this panel is his or her own child's best advocate.

My greatest hope today is that members of this committee and the audience will gain a better understanding of the unique nature of autism, the challenges and demands placed upon families caring for autistic children and adults, the significant emotional, financial, and community resources required to prepare and involve these individuals in everyday life, and to accept and respect these individuals for who they are.

However, as previously mentioned, I also come to this committee as a trained infectious disease specialist and clinical scientist and, therefore, feel compelled to comment on two other areas of importance to me. In the area of medical and other treatments intended to help autistic children function to the best of their ability, I would hope to see more funding to allow for appropriately controlled and conducted studies to rapidly determine the true effectiveness of these interventions so that families can make informed decisions regarding the best use of their limited resources, as we have heard from a number of the panel participants already. Without these studies, I and other parents of autistic children are forced to make decisions which may at times prove disadvantageous to all involved, without the benefits of real data.

I would also wish to comment on the current concerns regarding the potential causes for the perceived increase in autism. I implore the committee to be cautious in its statements and conclusions with regard to possible links to environmental factors and medical factors, especially immunizations. Recognizing that there are other parents on this panel who may feel otherwise—in fact, definitively feel otherwise—as a pediatric infectious disease specialist, I have seen no sound evidence linking autism to the MMR or any other vaccine, yet there is considerable evidence proving that the MMR vaccine is safe and highly effective in protecting children from serious diseases.

In closure, no matter what conclusions are formed today or where the activities of these hearings may lead, I would like to share an axiom of medicine I have learned, practice daily, and continue to teach to future doctors: Above all, do no harm.

Thank you.

Mr. BURTON. Thank you, Dr. Dankner.

[The prepared statement of Dr. Dankner follows:]

ORAL STATEMENT OF WAYNE M. DANKNER, M.D.

Honored committee members, fellow panel participants and members of the audience, I feel privileged today to appear before this committee to share my perspectives on autism, foremost as a parent but also from the additional perspectives as a pediatric infectious diseases specialist and a scientist engaged in clinical research and evidence-based medicine. My daughter Natalie, who is now nearly 13 years old, has autism and has taught my family and I a lot about ourselves and how the world around us deals with individuals who appear different from the "norm". She has been both a joy and a real challenge to live with and we continue to live through these experiences everyday. We have weathered this storm by rejoicing in her triumphs and finding the humor in past events even when those events may have seemed unbearable at that time. We have found that our daughter's greatest needs have been in the area of education and for a highly structured environment to allow her some control over the events of her life. It is in the area of education that we have experienced our greatest challenge and have been labeled by our local school district administrators as the most difficult parents they have had to deal with. In the context of the meeting that this statement was made, both my wife and I took it as an insult but have been convinced by our friends and family that we should wear it as a badge of honor. If anything, it highlights the advocacy we have championed for our daughter's rights to an appropriate education that addresses her individual needs and the manner in which she learns best. My greatest hope today is that members of this committee and the audience will gain a better understanding of the unique nature of autism; the challenges and demands placed upon families caring for autistic children and adults; the significant emotional, financial and community resources required to prepare and involve these individuals in everyday life; and to accept and respect these individuals for who they are.

However, as previously mentioned, I also come to this committee as a trained infectious diseases specialist and clinical scientist and therefore feel compelled to comment on two other areas of importance to me. In the area of medical and other treatments, intended to help autistic children function to the best of their ability, I would hope to see more funding to allow for appropriately controlled and conducted studies to rapidly determine the true effectiveness of these interventions so that families can make informed decisions regarding the best use of their limited resources. Without these studies, I and the other parents of autistic children are forced to make decisions, which may at times prove disadvantageous to all involved, without the benefits of real data.

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In closure, no matter what conclusions are formed today or where the activities of these hearings may lead, I would like to share an axiom of medicine I have both learned, practice daily, and continue to teach to future doctors; above all do no harm. Thank you.

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Mr. BURTON. First of all, I'll start with you, Dr. Dankner. Your daughter—whom I see sitting over there and is a lovely young lady—acquired her autistic condition—was this from birth?

Dr. DANKNER. No. She had the typical description that has been more commonly described of showing behaviors that became more and more obvious from about 14 to 18 months of age.

Mr. BURTON. When she was 14 months or thereabouts, did she receive any shots?

Dr. DANKNER. She received the normal vaccine schedule of immunizations as recommended by the American Academic of Pediatrics and the——

Mr. BURTON. What shots were those?

Dr. DANKNER. She received her MMR at about 15½ months of age.

Mr. BURTON. And when did she manifest or change?

Dr. DANKNER. She was manifesting subtle changes before that. It was obvious to us; we just did not know what to attribute it to at that time or what the issues were. We used to joke that compared to our older son, she seemed to be on an "independent study program."

Mr. BURTON. Did she receive any other shots when you started seeing the manifestation of autism?

Dr. DANKNER. She had received her previous shots at about 6 months of age.

Mr. BURTON. And had she received any others close to the time she started developing autism?

Dr. DANKNER. Not at that time, no.

Mr. BURTON. There were no other shots?

Dr. DANKNER. No, because at 12 months, essentially, you just get your PPD to screen for tuberculosis, which in California is potentially prevalent.

Mr. BURTON. When she started manifesting these signs, did she get worse after the MMR shot, or did it have any effect at all?

Dr. DANKNER. We did not notice any difference in her behavior; in fact, she got her second dose of MMR at about 5 years of age, and there was definitively no change in her behavior after that. She pretty much continued on in her mode of autistic behavior that required, in our opinion, a definitive educational approach to address her needs.

Mr. BURTON. Thank you, Doctor.

Mr. Bono, when did your child start manifesting signs of autism?

Mr. BONO. Within about 30 days of the MMR.

Mr. BURTON. So when did——

Mr. BONO. Quite honestly, when my wife had said, "Don't you see?" I think mothers have a much keener sense of behaviors with their infants.

Mr. BURTON. I understand, but what I am trying to find out is she received the MMR shot, and you and your wife started noticing a change——

Mr. BONO. Indeed; exactly.

Mr. BURTON [continuing]. In 30 days, you said?

Mr. BONO. Well, within hours of the shot, we went home, and there was no sleeping that night, and he had rashes on his body——

Mr. BURTON. And it got progressively worse?

Mr. BONO [continuing]. And over the next week, there were gastrointestinal problems, and finally, full blown behaviors that were odd.

Mr. BURTON. And how old was your child when that started?

Mr. BONO. I think it was right at 16 months.

Mr. BURTON. Sixteen months.

Ms. Smith, when did your child start manifesting a change in behavior?

Ms. SMITH. Well, at 16 months when they received the host of multiple vaccines, including the——

Mr. BURTON. Which were what? What were all those shots?

Ms. SMITH. The DPT, the Hib—it was their fourth DPT, their fourth Hib, their third hepatitis B, and their first MMR on that day—they came home, they slept for 24 hours, most of that time, did not eat a whole lot, long periods of sleep, had over 100-degree temperatures in spite of giving them Tylenol before the vaccine and during the entire 24 hours.

After that time, I figured, well, Jacob is sick again, because he was just kind of out of it and did not seem real interested in much——

Mr. BURTON. But this was at about 16 months——

Ms. SMITH. Right, right.

Mr. BURTON [continuing]. That you started seeing the manifest change in the child with autism.

Ms. SMITH. Right. And when we did go to the pediatrician, they just passed it off as his asserting his independence.

Mr. BURTON. OK.

Ms. Reynolds.

Ms. REYNOLDS. Liam got his shot on June 27, 1997. That is when he got his MMR and his Hib. That was the day before he turned 17 months old. A week later, I went to visit my parents in Maryville, TN for July 4th, and we started seeing some very strange, different behaviors showing up then. He would not come when we called his name. He was doing weird pattern movements up against the wall—but it was within a week.

Mr. BURTON. So it was right after he received the MMR shot.

Ms. REYNOLDS. Yes, sir.

Mr. BURTON. OK.

Mr. Smythe.

Mr. SMYTHE. At about 20 months, our son—I included in the record his vaccine schedule and my other children's, and interestingly, he was given hepatitis B the day he was born and then received the other two shots, one of them 30 days later, and another about 8 months later. He received 12 vaccines in the first 6 months, as the record shows, as compared to our other children who did not, in fact, receive the hepatitis B until a year after he received his third shot.

Mr. BURTON. When did he start——

Mr. SMYTHE. Right after the MMR, at 20 months.

Mr. BURTON. At 20 months, right after the MMR.

So you four people right here are all in concert that right after the MMR shot, you started seeing the manifest change in your children. Is that correct?

Ms. SMITH. Yes.

Mr. SMYTHE. Yes.

Ms. REYNOLDS. Yes.

Mr. BONO. Yes.

Mr. BURTON. And your child, Mr. Curtis?

Mr. CURTIS. I guess I have to be the dissenting opinion on this end of the table. I do not really remember the specific day of Morgan's MMR shots or any of his immunizations. He did not really exhibit any behaviors—it was not anything that he did—it was what he never did. It was the fact that he never talked. And again, as I mentioned, it was a very gradual process. I think his idiosyncratic behaviors of lining up his toys and the self-stimulatory behavior, the flapping of the hands, the spinning, all really started after he was 2 years old. It seemed like once we had a word for it, then it almost got worse.

We have thought about this a lot, because this is a very common theory. You read about it on the net, and you talk with other parents, and my wife and I have both discussed it at length, and we really do not see any correlation between the time of his immunizations and the onset of any specific or more intense behaviors.

Mr. BURTON. OK. My last question, then, would be did you notice shortly after his birth, as he was progressing, some problems then?

Mr. CURTIS. I think, yes. The reason I say "I think" is because we wanted to believe that he was a late talker, a late developer. The only thing we noticed was that he was not speaking and that he did not seem to react to the things that we did with him—but otherwise, he was a very normal, happy baby. He played, he interacted, he made lots of noises. He just never formed words and almost did not seem to react to our speech.

For a long time, we were very concerned about his hearing, that maybe he did not hear properly. In fact, when his hearing was tested, in the first test, they said he was deaf, and once they did the brainstem test that was conclusive, it turned out that his hearing was absolutely fine; it was just that he was not reacting to sound or voice.

Mr. BURTON. Thank you, Mr. Curtis, very much.

I want to yield—go ahead.

Mr. SMYTHE. I am sorry. I also noticed that my son was given the DPT vaccines the same day he was given the MMR. So he got six vaccines on the same day.

Ms. SMITH. So did mine.

Mr. SMYTHE. Yours did, also? OK.

Mr. BURTON. Thank you.

Mr. Waxman.

Mr. WAXMAN. It takes a lot of courage for all of you to be here, and I want you to know how much I appreciate it, especially when you are talking about something personal and painful. And, I know you are here to try to help us understand what you are going through so that we can try to find out about autism, and so that we can spare others from going through what you are going through.

There is legislation—this committee does not have legislative authority; it has the ability to hold hearings and get information. But the committee that has legislative jurisdiction, which I am also on, is the Commerce Committee, and there, we have a bill, H.R. 3301, which incorporates legislation by Congressman Greenwood, Congressman Bilirakis. Both Mr. Burton and I are on that bill, and it would do a lot to research more about the prevalence and ways to deal with autism. I hope that will give us some of these answers that we so desperately want.

Dr. Dankner, you are in a unique position. You are the father of an autistic child, and you are also a pediatrician and an expert on infectious diseases. But your testimony, is that you do not think there is sound evidence linking autism to the MMR vaccine. How can you say that when the other parents have given us evidence that, in their view, their children developed autism after the vaccine? Isn't that sound evidence? As a scientist, how do you think we should consider it, and what do we need to prove that there is a connection, if there is one?

Dr. DANKNER. One thing is that I am not here to invalidate the testimony of the other individuals. I know that from their heart, they feel that these events occurred in relation to a specific time and place, and it would be wrong for me to make a challenge to anyone on this panel. This is a personal issue for a number of these individuals.

However, as a clinical scientist, when we do research—I take care of HIV-infected children—it is important to identify causal events so that we do not do, as I mentioned, harm on either side of the fence of any of these issues. And I think it is important that if this committee or the scientific world feels that there is not enough evidence to generate a causal link between vaccinations and autism or any other disorder, those studies need to be done and that people then should look at those studies in a critical view, with appropriate peer review, and all individuals who are purporting one position versus another should be able to stand under the light of appropriate peer review to ensure that the scientific information is collected appropriately, analyzed appropriately, and discussed in an open forum and not in closed sessions, to ensure that the best information is provided to everyone so that, again, best decisions can be made by individuals.

I would like to bring a personal perspective as an infectious disease doctor. Unlike the other panel members, I have been on the other side of the fence and have seen children who have been harmed by vaccine-preventable diseases. I live close to the border, where the vaccination rate in Mexico is not the same as in the United States. I have seen children who have developed congenital rubella, a lifelong disabling condition. I have seen children die of measles during a measles epidemic in San Diego 10 years ago, even with the pretty reasonable vaccine rates for a highly transmissible disease. I have seen children suffer from pertussis, hospitalized at significant rates.

That position puts me in a position of being cautious about making any links, because if the vaccine rates fall in the United States, I can almost guarantee from my own personal experience that there will be individuals who will suffer on the other side of the fence, and those are the individuals that this committee usually does not hear about.

Mr. WAXMAN. I am not a scientist. I studied science at different levels of my education, and when I studied science, I was told that there is a scientific method to try to get answers, and the scientific method sometimes took a theory or a hypothesis and then tested it, and you had trials and control groups, and you tried to find out whether that theory is correct or not. Sometimes, theories turn out to be widely believed, but then they are discarded. We all studied the fact that in the past, people did not know about hygiene in connection with hospitals, which used to be among the most dangerous places to be because of the lack of hygiene.

But you are a scientist—the others on this panel are parents—but from a scientific method, are you saying the theory is absolutely incorrect, or are you saying that we just do not know enough to say that it is correct?

Dr. DANKNER. There are other people who will testify today who I think can probably better answer that. I was asked to come on the panel both as a parent and as a scientist.

My reading of what has been correlated to date does not appear to indicate a causal link. I think that debate has not been settled and probably needs to be, so that we do not continue to move down avenues that may be less productive in terms of the resources that are necessary to identify other potential links to autism, what the needs are in the community, which I can tell you are great——

Mr. WAXMAN. Let me interrupt you because my time is up. Are you saying to us, in other words, that we should not be alarmed about vaccinations and have parents refrain from having their kids vaccinated because of this theory, which, at this point, you do not think has gone through a scientific evaluation to be established as scientific fact?

Dr. DANKNER. I think an alarmist view is always of concern. I am a cautious individual, and I think we just need to be cautious in how we approach this issue.

Mr. BURTON. Thank you, Mr. Waxman.

Dr. Dankner, I hope that you will have the ability to stay and hear some of the other scientists' positions just for your own information.

Dr. DANKNER. I planned on it.

Mr. BURTON. Thank you very much.

Mrs. Morella.

Mrs. MORELLA. Thank you, Mr. Chairman.

I am very moved by the testimony that I have heard and read today. You are indeed the heroes, and we see you as role models, and your children are very fortunate to have you as parents. So thank you for being here.

I think the only question I want to ask is to Mr. Bono. When you said that you had to travel 12 hours for a 5-minute treatment—I do not know enough about the background to know what that treatment is, why you have to travel 12 hours for it, and how you found out about it.

Mr. BONO. I have to travel 12 hours, but that is deceiving, and first let me apologize. It is 6 hours up and 6 hours back in 1 day, so it is 12 hours.

Mrs. MORELLA. It is significant.

Mr. **BONO**. I have to travel because the treatment is not recognized as helping my son, and it is not approved. It is secretin, and they call it a slow push, or an infusion of sorts. We found that going up about every 28 days is a real good cycle for Jackson. Without it, he will not have a normal bowel movement; he will have acidic diarrhea, and he will not digest food properly, he will have unexplained rashes.

Mrs. **MORELLA**. Who advised you that this would help him in that area? Is there another doctor who made the suggestion?

Mr. **BONO**. At the press conference, one of the doctors said that the parents have really been the ones in the forefront of finding treatment options for their children, and this was a parent, too. Her name is Victoria Beck, and she serendipitously discovered secretin working for her child as the result of an endoscopy.

Laura and I had always thought there was some connection between the gut and the brain that needed to be bridged, and when we heard about Victoria's experience, we were rather fascinated, and we began to read about it, and that is how we arrived at that treatment.

Mrs. **MORELLA**. Dr. Dankner, I just want to briefly ask you—it is your daughter who is autistic, but in general, as I mentioned in my opening statement, there is a prevalence among males with regard to autism—are there some unique challenges that you face with a female rather than a male with autism?

Dr. **DANKNER**. Oh, yes, and those challenges are becoming more apparent now that she has achieved puberty. Luckily, she responds very well to sequenced pictures. One of the social stories that was provided to her through her school at my wife's insistence—and I have to admit that she has taken the forefront on this—is how to deal with menstruation. If you allow our daughter to do her own thing, she gets into a pattern, and that pattern becomes very difficult to break. And we have several holes in our wall for which we could probably pay a drywall person a pretty sum of money to repair when she gets mad at things, she will kick holes here and there. Luckily, we are having a room addition put on very soon, so that will take care of the last patch jobs that we did. That is one issue that came up.

Another issue that my wife and I feel very concerned about is the risk for her to be sexually abused as she gets older because of her inability to really indicate or express interactions with other individuals, as a number of the other panel discussants talked about with older children. Our daughter comes home from school, and you can ask her how her day went, and she will say "Fine," but you will not be able to—unless we are given a set of things that went on at school, she is not there to carry on small talk; that is not a major impetus in her life. She will interact with us because she has needs, and she will seek us out for those, but if left to her own devices, she will stay in her garage room, watch her TV, whatever video she finds the most appealing that day, and she loves to play with the reverse and replay buttons on a regular basis.

So, yes, I think there are some special challenges, but I think there are challenges for males growing up with autism also. There are things that they are going to have to face as they get older, and as they get older, I think the challenges become different. And I think all of the parents have to deal with the issue of what is going to happen to their children as they get older, who is going to take care of them when the parents are beyond an age when they can no longer take care of these children.

Mrs. MORELLA. The toll on parents is immeasurable, obviously. Thank you.

Thank you, Mr. Chairman.

Mr. BURTON. Thank you, Mrs. Morella.

Mr. Turner, do you have any questions?

Mr. TURNER. Thank you, Mr. Chairman.

Doctor, I just have one question for you, and I know this hearing centers on the problem of autism. The chairman has had personal experience with it in his family, and I know that he has also had some experience with a granddaughter with the hepatitis B vaccine.

I just wonder—is there any reason to question the age at which some of these vaccines are administered? I have always had the feeling that the younger the child, the more fragile, and therefore, the negative impact, if it be there, the potential is certainly greater when those vaccines are administered at an early age.

I have, of course, had particular interest in the hepatitis B vaccine which is administered, I think, in most States now at birth, routinely. In fact, I was in the home of a family in my district this weekend who have a 2-year-old child who is severely disabled, and basically, this family spends most of their waking hours tending to the child, and they strongly suspect that the problem is the result of a hepatitis B vaccination. That is administered at birth, and I have been told that there is really no logical argument for trying to vaccinate a newborn, because the threat of hepatitis B does not exist at that early an age, but it might be a more appropriate vaccine for later in childhood or approaching the teenage years.

Is there any reason to question the timing of some of these vaccines? One of our witnesses today talked about the large number of vaccines administered at one time.

Dr. DANKNER. Again, I was not called to the panel, I think, to give a long explanation of vaccine policy. There are lots of other individuals who have been involved in those policymaking decisions over the years. But I can give you my perspective once again from the diseases that we see in these age groups.

Albeit hepatitis B is an uncommon disease process that children may or may not get exposed to, the more likely exposure is going to occur when they reach sexual debut, as we call it, when they can easily be exposed to hepatitis B from a partner. That is one of the major concerns, and hepatitis B is a major cause of chronic liver disease in the United States and has reached a rate where vaccination would definitely have an impact on that disease in terms of its prevention.

The reason for giving some vaccines earlier is just to ensure that the vaccination gets performed. Rubella is a perfect example. When congenital rubella was identified in the United States, Australia and Europe as a devastating disease linked definitively to the acquisition of rubella by mothers who were previously uninfected, with no previous immunity to rubella, the approach was taken differently by different nations. If you look at the United States, they focused on giving the rubella vaccine early in life so that you would eliminate the pool of individuals who were exposing adults to rubella, whereas England took the approach of trying to vaccinate adolescent females primarily, because they were the, "at-risk population" who could transmit rubella to their unborn fetus. The experience in England was that it took them a lot longer to eliminate congenital rubella from their population, and the experience in the United States was an enormous success, because even though you had women who were susceptible to rubella, they were not being exposed, and as those children who got the rubella vaccine early in life aged up into their childbearing years, they were no longer at risk of developing congenital rubella. The result is that the United States sees probably about two, four, five cases of congenital rubella a year, and most of those are from individuals who have either not received vaccination or come from a foreign country where the vaccine rates are much lower.

Additionally, the hemophilus influenza B vaccine, the vast majority of H-flu meningitis that we see occurred in children less than 24 months of age. If you wait until they are 2 years of age to give the vaccine, you have missed the peak period. We used to see at our Children's Hospital in San Diego 60 to 70 cases of hemophilus influenza meningitis per year. That is a pretty devastating disease for most of the children. We see essentially one case about every 2 or 3 years now, and the last case we saw was in a mother who had her fourth child and just did not get to the doctor to get the H-flu vaccine.

I think that if you want to ask about the policies, you will need to talk to the policymakers for their conclusions. I can only give you my viewpoint from the standpoint of how I see infectious disease and the impact that I have seen in our local community, and the diseases that I no longer see, which some doctors in practice now may never see again, I think to the advantage of those particular children who are not suffering from those particular diseases.

To be fair to the other panel participants, I recognize that I am a physician and I bring certain issues to the table, but I think the other individuals also have a lot to say that needs to be heard, and I do not want to monopolize everyone's time.

Mr. TURNER. I appreciate your comments. I guess the only point I was trying to make, and perhaps the witnesses on our second panel will help us with it, is that there are obviously good public policy reasons to have the vaccines given, but at a minimum, if the timing of those vaccines could be later in life for children, it seems that at least we owe the public that information, because particularly in the case of hepatitis B, if the threat of hepatitis B only occurs at the time when the child has the potential of becoming sexually active, it does not make a lot of sense to have a public policy that says we administer it on the second day of life; and if there is a risk, I as a parent certainly would not want that vaccine administered to my child at that point in time. People need to have that information.

Thank you so much, Doctor.

Mr. BURTON. The gentleman's time has expired.

Mr. TURNER. Thank you, Mr. Chairman.

Mr. BURTON. Thank you very much, Mr. Turner.

Mr. LaTourette.

Mr. LATOURETTE. Thank you, Mr. Chairman, and thank you, Mr. Waxman.

I want to thank each of you for sharing your families' experiences with us today. Ms. Smith, my wife and I are the parents of 8-year-old twins, and we always said that if the twins had been first, they would have been last, because raising twins is enough of a challenge all by itself.

I was not going to talk about what my friend from Texas was talking about, but it always amazed me—and I am not smart enough to know the connection between vaccines and what brings you here today—but it always amazed me that after these vaccines, you would bring your baby home, and he would turn bright red and have a horrible fever, and they would say, "Well, you just have to hang on for a little while, and everything is going to be OK," and this was a drug which was going to prevent some horrible childhood disease in the future. But why they were being exposed to these vaccines within the first couple days of being born, or even the first few months of being born, is something that I do think we need to get a handle on.

But Ms. Smith, I want to talk to you about a portion of your testimony, and Ms. Reynolds also, because if I understand it, you may be following similar paths. That is, you have had Jacob screened and tested for the presence of heavy metals and fungi and other foreign substances within his system, and he is currently undergoing some nutritional therapy and so on. I wonder if you could share those experiences with us. And I think it was you, Ms. Smith, who wrote that the results of that screening were shocking and that it was amazing—was it you who had Dr. Stephanie Cave——

Ms. SMITH. Yes. We both——

Mr. LATOURETTE. You both had Dr. Stephanie Cave.

Ms. SMITH. Right.

Mr. LATOURETTE. OK. Then, maybe one at a time or in tandem, you could tell us a little bit about Dr. Cave's work and what about the results of these screenings was shocking, and what sorts of things now Liam and Jacob are going through that give you hope and point in the direction that this is a biomedical condition rather than a neurological condition.

Ms. SMITH. In my case, it is clearly not a genetic issue, considering that they are identical. The other reason I do not feel that it was a neurological disorder that he was born with is because his descent into autism happened so rapidly. He was completely with me, and he descended into autism so rapidly, and to me, that is not a neurological disorder that he had at birth.

Also, I feel that it was not a neurological disorder that he was born with because when he was 2½, we had several professionals recommend that we put him on medications. I do not know what medications they said, such as Ritalin—I never pursued that avenue, because I felt like medicating a 2½ child was simply not good enough when I did not know what his body was already doing.

I went to see Dr. Cave, and she ran blood and urine tests and took stool samples to see what deficiencies he had, the areas that he was lacking in, his amino acids and so on. We found that he had 10 food allergies. Because he had been on repeated antibiotics, he had extremely high—out of 23 fungal and yeast infections, he was high in 20. He was chromium, zinc, magnesium and copper deficient. He was B5-deficient. So, basically, what we did was we immediately started taking out what was bad and putting back what was good and taking him off the foods that he was allergic to. And within 5 days, my son, who had only a couple of words in his language and was very lost, said a full, appropriate sentence and started speaking again.

So the rapid improvement also shows me that this was not a neurological disorder in his case.

Mr. LATOURETTE. OK. And Ms. Reynolds, is Liam also undergoing similar therapy?

Ms. REYNOLDS. Yes, he is. When he was diagnosed in May 1998, we put him on a strict, gluten-free, casein-free diet that Dr. Cave prescribed, where he was not allowed to eat any of the substances, because his body was taking those things and actually manufacturing morphine, which was what was making him just sit and stare and not respond appropriately to things.

Since that time, he has undergone an MRI, EEGs, all the normal things that they run on autistic children, and those all point to normal things. But when you start doing blood work and stool work and urinalysis, and they measured for toxic metals in his hair, she suggested that we give him a medication that would help pull out the heavy metals that he had been exposed to, and my husband and I were so gun-shy at this point from dealing with doctors that we pulled out the PDR and read through it, and we were, like, "I do not know, this sounds a little weird to me; I do not think we are going to try this." And we took Liam to an environmental toxicologist who did some blood work and told us that the shape of Liam's blood—he had stippled cells that would be the same as a plant worker who had had serious toxic heavy metal exposure and that our son's blood cells were malformed as a result of heavy metal exposure that he had received.

We have given him this medication several times. We were able in December to get a good urine sample, which is a little challenging around our house, and we were finally able to test that. The normal range—and I am probably going to mess this up—but the normal range for anything to show up in their bodies is between zero and six, and his lead and mercury had reduced down to normal ranges, but his levels of tin were completely off the charts. They were not even measurable. They were up around 250.

Mr. LATOURETTE. Did you say tin?

Ms. REYNOLDS. Tin.

Mr. LATOURETTE. If I could just beg the chairman's indulgence, is he likewise receiving, aside from the medication that you are talking about, a nutritional program?

Ms. REYNOLDS. He receives a number of nutritional supplements every day. He is on an antifungal medication, because we have been dealing with a yeast infection that just will not go away for 3 years, that makes him just a real mess. He is just a walking biological nightmare. And he looks as healthy as a horse. He has great skin, he has great teeth and cheeks. He is a beautiful, beautiful little boy, but if you take it down to the cellular and the molecular level, you can see that this child is a total mess.

Mr. LATOURETTE. Thank you very much.

Thank you, Mr. Chairman.

Ms. REYNOLDS. You are welcome.

Mr. BURTON. Thank you very much, Mr. LaTourette.

Ms. Biggert, did you have any questions?

Ms. BIGGERT. No questions, Mr. Chairman.

Mr. BURTON. Well, let me thank this panel. I just want to say to the four of you who have experienced this change right after the MMR shot that my daughter is sitting back there, and I and my daughter experienced exactly the same things that you did, and I believe what you are saying, and we are going to pursue that as diligently as possible, because I cannot believe that it is just a coincidence that the shot is given, and within a very short time—he got nine shots in 1 day, the MMR and DPAT, HIB and oral polio—and within a matter of just a few days, instead of being the normal child that we played with and talked to and everything else, he was running around, banging his head against the wall and flailing his arms.

When people tell me that that was a genetic problem, I am telling you they are just nuts. That is not the way it was.

With that, I want to thank this panel very much. We will now go to our next panel.

Thank you very much.

We now welcome our second panel to the witness table. This panel consists of: Dr. Andrew Wakefield, who came all the way from merry old England, and we appreciate him being here; Professor John O'Leary, whom I am sure you will notice after he starts talking is from Ireland; Dr. Vijendra Singh, I appreciate you being here; Dr. Coleen Boyle, Dr. Paul Offit, and Dr. Brent Taylor.

Would you all please rise and be sworn?

[Witnesses sworn.]

Mr. BURTON. Please have a seat.

Dr. Wakefield, would you like to start this panel?

STATEMENTS OF DR. ANDREW WAKEFIELD, ROYAL FREE AND UNIVERSITY COLLEGE MEDICAL SCHOOL, LONDON, ENGLAND; DR. JOHN O'LEARY, COOMBE WOMEN'S HOSPITAL, DUBLIN, IRELAND; VIJENDRA K. SINGH, UTAH STATE UNIVERSITY; COLEEN A. BOYLE, CENTERS FOR DISEASE CONTROL AND PREVENTION, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, ACCOMPANIED BY DR. BEN SCHWARTZ, ACTING DIRECTOR, EPIDEMIOLOGY AND SURVEILLANCE DIVISION, CDC; DR. PAUL A. OFFIT, UNIVERSITY OF PENNSYLVANIA SCHOOL OF MEDICINE; AND DR. BRENT TAYLOR, ROYAL FREE AND UNIVERSITY COLLEGE MEDICAL SCHOOL, LONDON, ENGLAND

Dr. WAKEFIELD. Yes, thank you, Mr. Chairman, members of the committee. It is a great privilege to be here.

The purpose of my testimony is to report the results of the clinical and scientific investigation of a series of children with autism. Nothing in this testimony should be construed as anti-vaccine; rather, I advocate the safest vaccination strategies for the protection of children and the control of communicable disease. I am also here on my behalf representing the children who have come to me for investigation.

I would like you to look at the screen if you would, please, and I will take you through the presentation.

Next slide, please.

Just as a little bit of background, this represents 12 years of intensive clinical and scientific research, collaborative research, into the causes and mechanisms of bowel inflammation. I am a gastroenterologist.

The principal authors of this work have contributed to over 1,500 peer-reviewed and published scientific papers and abstracts. Again, these represent my views.

Next slide, please.

I want to report the results today from the first 60 children that we have investigated. We have now investigated over 150 children, and the results that I am going to describe are pertinent to all those children bar about four.

As far as the range of psychiatric assessments, the great majority had autism, but there was a spectrum of neuropsychiatric problems including Asperger's Syndrome and Attention Deficit Disorder. By far and away the most important investigation has been direct visualization of the bowel and taking biopsies by the procedure of ileocolonoscopy. This is a flexible instrument introduced into the bottom end to take a biopsy.

Next slide, please.

What you have heard this morning is a classical description of two different types of autism from the parents. You have heard about the children that we have seen, those who have gone off after a period of normal development, many of them in the face of multiple vaccine exposures with severe gastrointestinal symptoms.

The other type, described very articulately, was of an insidious failure to acquire skills at an extremely important point. The essence of what I am going to present today is based upon conventional clinical medicine. It is listening to the patient.

Here is a child who was entirely normal for the first year of life and went off a week after receiving his MMR vaccine. He is exactly as the four children were described earlier.

Next slide, please.

The classical features in these children are pain—there is a radiograph here of the abdomen, and there is fecal impaction. When these children came to us, the feature was of diarrhea, but in fact this turned out to be what we call spurious or overflow diarrhea. There was soiling, loss of contents, fastidious eating habits, reflux and nighttime wakening. They get heartburn, and they wake up very distressed. These symptoms are the same wherever you go. If I listen to parents from Canada, from the States, from Europe, and from Australia, the story is the same.

Next slide, please.

The associated features that we have in these children are of atopy—asthma, eczema, and hay fever. There are refractory upper respiratory tract infections. They do not deal well with common childhood infections, colds, and there is a very high level of autoimmune disease in the family—thyroid disease, diabetes, for example.

Next slide, please.

This is the insider's view of the small intestine. The panel on the top left is of what it should look like in a child. The bottom left of is lymphoid nodular hyperplasia. There is a swelling of the lymph glands in the bowel. These are rather like tonsils, and when they swell, they cause pain and symptoms.

Mr. Waxman asked about the reproducibility. He is absolutely right. Up on the top right-hand panel, you see a child who was scoped in the United States with exactly the same symptoms. So this is reproducible in two different continents. We have compared it with controls, and the graph on the bottom right shows that even children who come to us with gastrointestinal symptoms who are scoped, the finding of lymphoid nodular hyperplasia is relatively uncommon. In the bar on the left, 85 percent of them show no evidence of it, but virtually all of our autistic children show evidence of lymphoid hyperplasia, either mild, moderate, or severe.

Next slide, please.

There are histological changes under microscopy which show there is a definite disease. The top left-hand panel is normal; the bottom right-hand panel, for example, shows what is called a crypt abscess, that is, puss in the bowel wall, and this is a feature that we see in children and adults with ulcerative colitis. There is a clear and demonstrable, albeit subtle, pathology.

Next slide, please.

A further paper that is due to be published soon has taken this to one further level and asked is this disease distinct from classical inflammatory bowel disease, Crohn's and colitis, or is it something new. And the data, at least, so far, suggest that it is something new.

Next slide, please.

We have described this feature in the gut, lymphoid hyperplasia, and colitis in children with autism. From this same city, from Georgetown University, Professor Joe Bellanti has described it in children with attention deficit disorder, coming back to the question, is this a spectrum of disorders which have at their heart some gastrointestinal abnormality.

Next slide, please.

Lymphoid nodular hyperplasia classically occurs in the presence of immunodeficiency. We do see it during acute infection, but it is classically associated with immunodeficiency. Are our children immunodeficient? As a group, the answer is yes, they are.

This graph just shows you a particular count of a certain type of immune cell in the blood. The green line is the upper limit for normal, the red line is the lower limit for normal, and each blue dot represents a child. You can see that the great majority sit at or below the lower limit of normal. Not only are they numerically deficient, their immune system does not respond appropriately to common recall antigens when compared with normal age-matched children. In other words, if you give them a skin-prick test for pertussis or diphtheria, they mount no response.

Next slide, please.

So the key features of the syndrome are developmental regression, ileocolonic lymphoid hyperplasia, swelling of these tonsil tissues, enterocolitis—that means inflammation of the small and large intestines—and immunodeficiency.

Next slide, please.

So it is a real syndrome, there is a remarkably consistent pattern of bowel inflammation, and it provides us with vital clues. What are those clues?

Next slide, please.

The story as told to us and which we have an obligation to report is that the majority of children regressed following a period of normal development in the face of MMR vaccination. That does not mean it is the cause of the disease.

We also had two children who regressed after classical measles infection—one after the monovalent measles vaccine and one after a rare vasculitic rash. Thirty-six percent of parents could contemporaneously identify no particular environmental hit.

Next slide, please.

Have measles and common childhood infections been linked to autism before? Is there a reason to go into this and look at it? The answer is yes, there is. There is a paper that came from the Harvard School of Public Health, and it showed that atypical patterns of exposure to common childhood infections—measles, mumps, chicken pox, rubella—were a risk for autism in the child. By "atypical," I mean maternal exposure when pregnant or neonatal exposure.

What was intriguing about this, which we may come to later, is that if you were a pregnant mother who was exposed to more than one of these common infections at the same time, or indeed, an infant child, then your risk of autism was both greater, and the severity of the autism was greater. Question: Was there a compound effect of more than one infection?

It has also been shown that children born in and around epidemics of measles and rubella have higher rates of this disease.

Next slide, please.

What about vaccines? There is a paper from the Vaccine Damage Compensation Board in the United States—acute encephalopathy followed by permanent brain injury or death associated with further attenuated measles vaccine. What was intriguing in this cohort of children who fulfilled rather strict criteria was that 43 out of 48 underwent developmental regression as part of their syndrome. So we have this other pattern of exposure to measles as the further attenuated vaccine children undergoing developmental regression.

Next slide, please.

To summarize, unusual patterns of exposure to common childhood infections are associated with autism and developmental regression.

Next slide, please.

Here is the clue. This is the important image, and here, you see the insider's view again—these swollen tonsilar tissues. If you are looking for an infection, this is where you should be looking.

Next slide, please.

When you look down the microscope, this is what that swollen tonsil tissue looks like, and you are looking in the center of that for the infection. This is a response to a foreign agent, a foreign antigen, usually an infection. So if you are looking for the cause of that, that is where you are looking.

Next slide, please.

This is a very high-powered micrograph of a single cell called a follicular dendritic cell, and this is crucial, because if you are looking for the source of that infection, not only are you looking in that lymphoid follicle, not only in the center of the lymphoid follicle, but in this specific cell.

Next slide, please.

When we look in that specific cell using an antibody which picks up measles protein and only measles protein, we find it in that cell. We do not find it in other cells or other tissue, we find it in that cell.

Next slide, please.

You look for other viruses. You ask the question: Is this just a nonspecific response? Do we find other viruses in there? So you look for adenovirus, herpes simplex I and II, rubella, mumps, HIV, and other crucial controls that Mr. Waxman referred to early, and you do not find them. They are not there.

So at least within the context of this study, this appears to be specific for measles virus.

Next slide, please.

The next question: Is there an antibody; is there an immune response to the virus in these children? The mere presence does not make it the cause. Is there an immune response?

We take the autistic children, and we compare them with age-matched controls, and we look at measles antibody titers. We also look at controls of mumps, rubella, and cytomegalur virus, or other common childhood infections. The only one for which there is a statistically significant difference between the cases and the controls is for the measles virus.

Next slide, please.

We had failed completely to identify this virus by molecular amplification technology. In my laboratory, we had a reaction that was sensitive to about 10,000 copies. Anything less, we could not find it.

The Japanese had succeeded, so we sent nine blood samples from our children to the Japanese laboratory, and we also sent 21 other patients. We mixed them up. We did not tell them what they were getting. They just had a control label. And they identified measles virus in three of those nine children in the peripheral blood. That is an intriguing finding. This is consistent with; but not definitely, vaccine strain. One can only say that this is consistent with, but there it is, and this was a blinded control study.

Next slide, please.

Very briefly, to finish up, what is the link between the gut and the brain? This is one of the most difficult things for people to understand. How can the gut influence the brain? I come from a liver unit where we see patients with chronic liver failure, acute liver failure, all the time, and one of the classical manifestations of that—next slide, please—is hepatic encephalopathy. This is where the liver is damaged, is diseased, and fails to degrade the chemical constituents of the bowel that come through. It fails to mop them up and clear them out; they impact upon the brain. This is largely reversible. If you are hit with these for long enough, it becomes irreversible.

The question is, therefore—at least we have biologically a plausible hypothesis, a testable hypothesis that elements from the gut, undegraded chemicals from the gut, including the opiods that were referred to by Shelley Reynolds, may be getting through, may not be metabolized, may be impacting upon the rapidly developing brain during the first few years of life and producing residual cognitive deficit, which we recognize as autism.

Next slide, please.

So finally, in summary, we have an environmental insult in perhaps a genetically susceptible child. The problem is that if you go to Sweden now, autism affects over 1.2 percent of the pediatric population. So if there is a genetic background, it is clearly widely distributed within the population. We believe that in many children, clearly, the subset of autistics, it leads to gut infection and damage; that leads to an ingress, an impaired metabolism, degradation of these chemicals from the gut which then get through and impact upon the brain. And the disregulated immune system which measles classically can produce also encourages immune diseases, atopic diseases, and immuno disregulation.

Thank you, Mr. Chairman.

Mr. BURTON. Thank you, Doctor.

Professor O'Leary.

[The prepared statement of Dr. Wakefield follows:]

Testimony before Congressional Oversight Committee on Autism and Immunisation

Dr Andrew J Wakefield MB.,BS FRCS

Mr Chairman and members of the Committee,

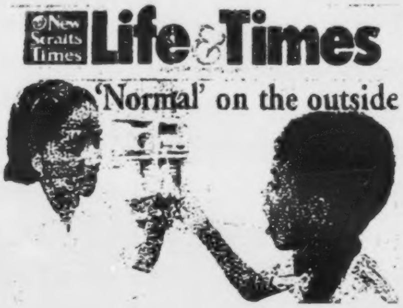
The purpose of this testimony is to report the results of the clinical and scientific investigation in a series of children with developmental disorders, principally autism. Nothing in this testimony should be construed as anti-vaccine; rather the author advocates the safest vaccination strategies for the protection of children and the control of communicable disease. The opinions expressed in both this text and the attendant presentation, represent those of the author. I am testifying on behalf of the children who have been referred to me for investigation, and am not here on behalf of, or representing, any institution.

These studies were undertaken against a collective background experience of the principal authors, of over 500 peer-reviewed clinical and scientific papers, published in reputable medical journals, and over 1000 peer reviewed abstracts presented to learned societies. The ongoing studies form part of an international, multidisciplinary research program including California's MIND Institute at UC Davis into inflammatory diseases of the intestine and childhood developmental disorders, involving the disciplines of pathology, immunology, virology (particularly, molecular detection of viral genes) and epidemiology. All studies were approved by the appropriate institutional Ethical Practices Committee.

We have now investigated over 150 affected children with autistic spectrum disorders. A preliminary report of the first 12 children has been published (*Lancet* 1998;351:637-641). A detailed analysis of the first 60 children in due to be published (*American Journal of Gastroenterology*). The clinical findings described in these reports have been reproduced in the extended study of more than 150 children. The latter group includes 4 children from the US. Independently, other centres investigating children with autism and gastrointestinal symptoms in the UK, Europe and the US, have confirmed the clinical findings that comprise the syndrome of *autistic enterocolitis*.

Our study was initiated at the request of parents, and was stimulated by the conviction that their children had; 1) developed normally during the first 1-2 years of life; 2) undergone developmental regression to autism, in the majority of cases following measles mumps rubella (MMR) vaccination, and; 3) developed gastrointestinal symptoms that, in the parents' opinion, were closely associated with the behavioral/developmental pathology. Almost without exception, the anxieties of the parents, as described above, had been dismissed by the medical and allied professions. Bowel symptoms had been disregarded without investigation. Raising the issue of the possible role of MMR vaccine in their child's autistic regression had led to an acrimonious breakdown of the doctor-parent relationship in many cases.

One of the fundamental rules of conventional clinical medicine is to listen; to listen to the patient or the patient's parents, and then to investigate the presenting symptoms, without prejudice, in order to determine whether or not they have an organic origin. In this context, the Committee should be aware that the parents' story is remarkably consistent whether, for example, they come from the US, Canada, the UK, mainland Europe, Asia or Australia. The pervasive features include developmental regression and gastrointestinal symptoms following MMR vaccination (Figure 1).



New Straits Times Life & Times

'Normal' on the outside

Figure 1 *New Straits Times*, Kuala Lumpur
"After receiving his MMR inoculation at 18 months, Nicholas came down with a very bad case of gastroenteritis. From then on I noticed very distinct changes in his behavior," Ang recounts.

Accordingly, we have conducted a series of detailed studies on behalf of these children, the findings of which, in summary form, include:

1. A pattern of symptoms that comprise abdominal pain, abnormal bowel habit (constipation with overflow diarrhoea), bloating, reflux. The pattern and severity of behavioural and gastrointestinal symptoms appear to parallel each other.

2. A frequent history of atopy (asthma, eczema, hay fever)

3. Recurrent, refractory upper respiratory tract/ear infections.

4. A strong family history of autoimmune disease.

5. On direct visualisation of the lower intestine, ileo-colonic lymphoid nodular hyperplasia (swelling of the tonsil-like tissues in the small and large intestine; figure 2), plus inflammation of the colon and, to a lesser extent, the ileum.

Figure 2. Marked lymphoid nodular hyperplasia of the terminal ileum in a child with autistic enterocolitis

6. Low numbers of circulating immune cells (lymphocytes; figure 3) and an inability to respond appropriately to common antigens to which the children have been exposed previously (tetanus, diptheria, pertussis, house dust mite, candida). These differences are statistically significant compared with age-matched healthy controls.

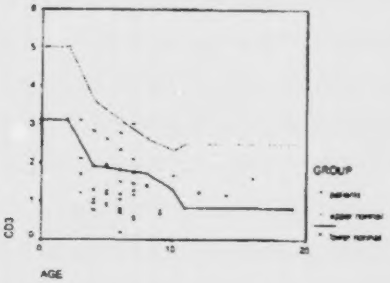


Figure 3. CD3+ lymphocyte counts in peripheral blood of autistic children (each blue square represents one child) compared with age-standardised reference ranges, showing the upper (green) and lower (red) limits of normal (5th – 95th centiles)

7. Microscopically, in intestinal biopsy tissue, a specific and subtle inflammatory pathology in the colon (figures 4 & 5) that, overall, appears distinct from that seen in patients with Crohn's disease, ulcerative colitis, idiopathic constipation, and histologically normal controls of a similar age.

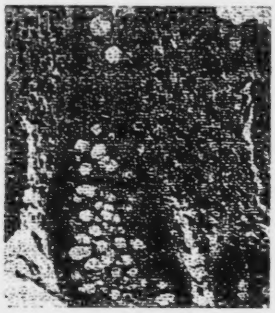


Figure 4. Autistic enterocolitis: acute inflammation in a colonic crypt

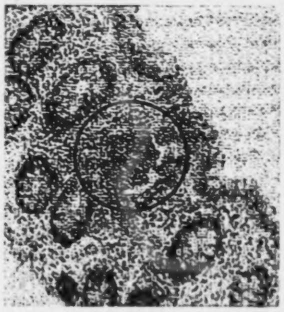


Figure 5. Autistic enterocolitis: colonic crypt abcess within the black circle

8. A pattern of colonic inflammation that distinguishes *autistic enterocolitis* from other common forms of inflammatory bowel disease, as demonstrated by the detection and quantification of specific immune and inflammatory molecules in the intestinal lining.

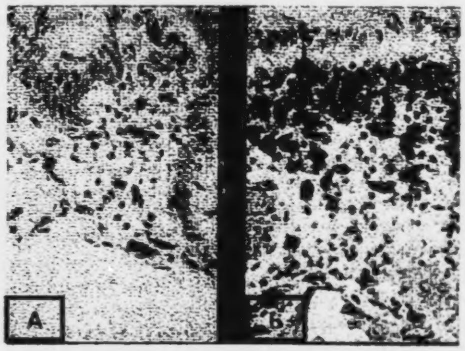


Figure 6. Activation of the immune system in the bowel lining in autistic enterocolitis. A = normal child; B = autistic enterocolitis. Staining represents Class II antigen expression (LN3)

1. In blood, a raised circulating IgG measles antibody titre that is statistically significant when compared with age-matched healthy controls. The same is not seen for antibodies to mumps, rubella or cytomegalovirus.

2. In preliminary studies, the presence in intestinal tissues, of measles-specific antigens (protein), specifically in the follicular dendritic cells of the reactive ileal lymphoid tissue.

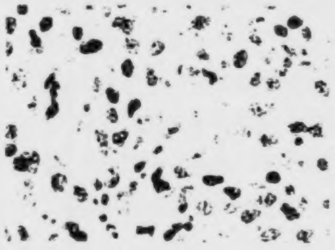


Figure 5. Measles virus nucleocapsid protein in the centre of a reactive lymphoid follicle in a child with autistic enterocolitis

3.The absence, in the same lymphoid tissues, of antigens specific for other common viruses including mumps, rubella, adenovirus, herpes simplex virus I and II and HIV.

4. The absence of measles antigen, in intestinal lymphoid tissue from developmentally normal children without inflammatory pathology.

5. Investigations including chromosome analysis, metabolic analysis, imaging studies of the central nervous system, electro-encephalography and analysis of cerebrospinal fluid did not reveal any alternative causes for developmental regression in these children.

6. The presence in 3 of the initial 9 children with autistic enterocolitis who were studied by gene amplification technology, of measles virus hemagglutinin (H)

gene in peripheral blood immune cells (Kawashima H et al. *Digestive Diseases and Sciences*. March 2000)

7. Subsequent molecular studies of the detection of measles virus genetic material will be described by Professor J.J. O'Leary.

The issue of coincidence

Many pediatricians have expressed the opinion that, for autism, any association between MMR vaccination and the parents' recognition of the child's behavioral problems is coincidental. Such an assumption is inappropriate in the absence of a thorough history and investigation. For example, symptoms of classical, early onset autism are often noticed initially, in the first and second years of life the child does not develop in the way of normal siblings and peers. Parental concerns about the child's development are often expressed in the second year, when these differences become evident. MMR vaccine is given routinely at this age, and coincidence is therefore inevitable. However, in children with autistic regression, the pattern is of loss of speech, language and social skills, accompanied by bizarre behaviors, in a previously developmentally normal child. This is consistent with an early onset disintegrative psychosis. Furthermore, loss of speech and language are accompanied by symptoms of excessive thirst, bowel disturbances, self-injury, and a self-limited diet associated with cravings for particular foods. Atopy and recurrent, refractory upper respiratory tract infections are prominent features. These symptoms do not feature in the exclusively behavioral descriptors of the diagnostic manual for autism - DSM-IV.

The issue of coincidence may be addressed, in part, by considering those children who have received more than one, measles containing vaccine. If the intestinal pathology and the associated behavioral problems are causally linked to a persistent viral infection of the intestine, then re-exposure to the same virus vaccine might be expected to exacerbate the condition by, for example, eliciting an immune response against virally infected cells. In the cohort of children with autistic enterocolitis under our care, we have 10 children who have received more than one dose of a measles containing vaccine. Developmental/behavioral changes had to be identified contemporaneously, rather than retrospectively. The data for first and second vaccine doses, and initial and subsequent behavioral changes are shown graphically, below (Figure 7).

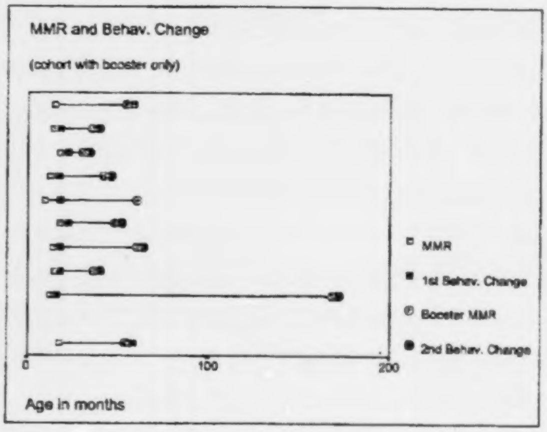


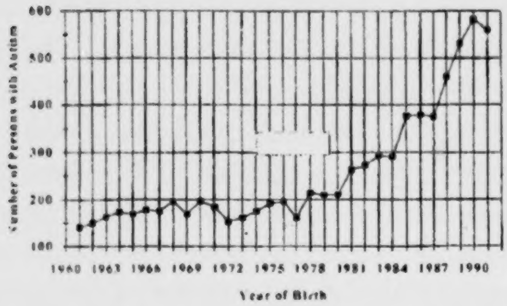
Figure 7. The graph, where each time line represents one child, shows that for 7 children (2-4 & 6-9) developmental regression accompanied both exposures. In 2 children (1 & 10) it followed the second dose, long after the second year of life. These data are not consistent with coincidence.

Temporal trends in autism

If MMR vaccine is causally related to autism and autistic enterocolitis, then there should have been an increase in the numbers of cases of autism following the introduction of MMR vaccine in different countries. Moreover, since MMR was introduced into different countries at different times, the effect should be one of

Is Incidence Increasing?

Birth Year of Patients with Autism



Temporal trends for autsim cases in California

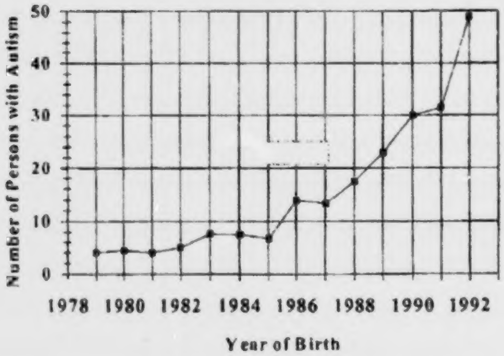
A dramatic rise in the numbers of new cases of autism seen in the first birth cohorts eligible for MMR vaccination (bar)

There was a rather protracted period over which MMR was introduced in the US, because of the continued availability of monovalent vaccines. (F.Yazback. personal communication)

Source: Office of Developmental Services, Sacramento, Ca.

similar temporal trends in different countries, with any increase corresponding with the introduction of MMR.

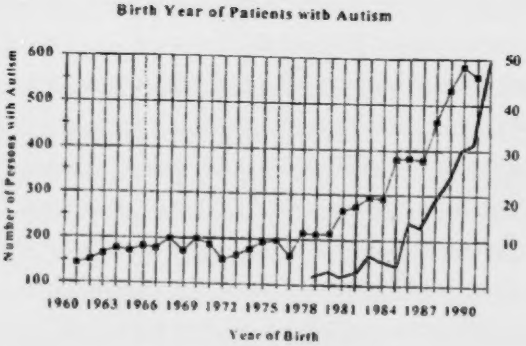
Autism cases under 60 months of age by year of birth, 1979-1992.



Temporal trends for autism U.K. North London

Data published in the Lancet, compiled by the Public Health Laboratory Services and the Department of Community Paediatrics, Royal Free Hospital. Data show a doubling of autsim cases in the first birth cohorts eligible for MMR, with a dramatic and sustained rise thereafter. Bar shows first birth cohorts eligible for MMR

Source: Taylor et al. Lancet,



Temporal trend for autism: US and UK

Superimposing the data for the US and the UK analyses described above, identical time trends are seen, with a delay in the rise in the UK that corresponds to the later in introduction of the MMR vaccine in 1988

It is important to note that the UK and the US use exactly the same diagnostic criteria for autism and yet there is a 10-year delay in rise in the number of cases. These changes are very unlikely to reflect artefacts due to changing diagnostic criteria. This is confirmed by reviewing the temporal trends for autism and learning disabled children in the state of Illinois from 1991-1997.

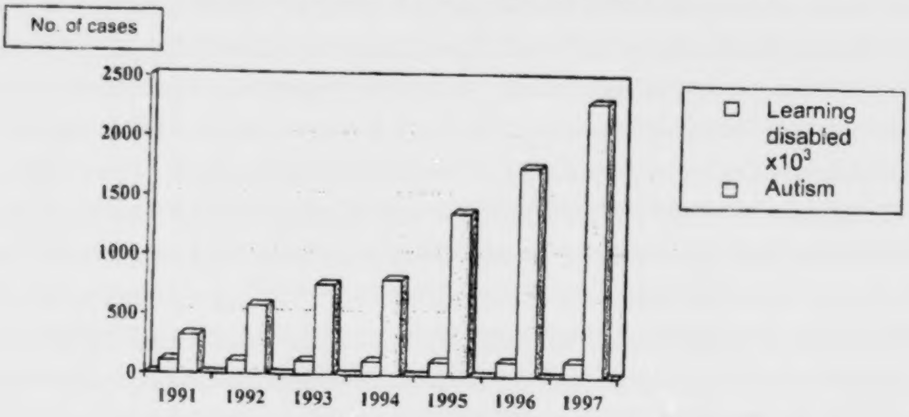


Figure 12. Temporal trends for autism and learning disabled (x10^3) in Illinois. In 1994 the broader autism criteria of DSM.III Revised (DSM.III-R) were amended

to the more exclusive DSM-IV. Had the increase been an artefact of diagnosis, then the numbers should have levelled off beyond 1994.

The Finnish paper

No evidence for MMR-associated inflammatory bowel disease or autism in a 14-year prospective study. Peltola et al, *Lancet* 1998; **351**: 1327-1328.

The study:

- Identified adverse events following 3 million doses of MMR in Finland during the 3 weeks post-vaccination
- Traced those individuals with severe gastrointestinal symptoms (diarrhea /vomiting) after MMR, lasting 24hrs or more. There were 31 recorded episodes.
- Followed up those 31 individuals from 1 to 14 years (mean=9 years) after MMR
- None of the 31 children had a diagnosis of autism or inflammatory bowel disease

The problems

- No one has ever suggested that acute gastrointestinal symptoms within 3 weeks of MMR is a risk for autism or inflammatory bowel disease.
- Parents reported **behavioural changes** as the initial presenting feature in their children
- 31 children is far too small a number, and the children are still too young to assess risk of inflammatory bowel disease.

Conclusion

- Peltola et al tested the wrong hypothesis

The Taylor paper

Taylor B et al (Royal Free & University College Medical School & the Public Health Laboratory Service) published a paper (*Lancet* 1999;353:2026-2029) that sought to dispel any relationship between MMR vaccine and autism. They performed a Case-Series analysis of children with autism in North West Thames. **Reasoning:** If there is a causal association between MMR and autism, there should have been a step-up in the numbers of children with autism in the first birth cohorts eligible for MMR. The authors stated that such a step-up should have occurred in those born in 1987 since these were the first children eligible to receive MMR in the second year of life. There was a crucial omission from the paper by Taylor et al. In 1988 – with the introduction of the MMR in the UK – a "Catch-Up" campaign was instituted which targeted pre-school children of one to four years of age who had not previously received monovalent measles, mumps or rubella vaccines irrespective of their immunity to the three infections.

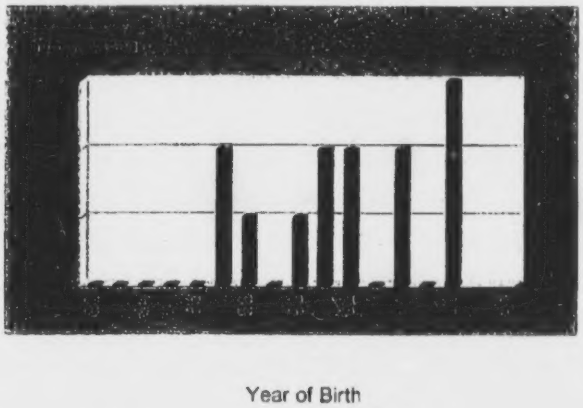
Corroboration of this comes in the form of a contemporaneous paper from Dr Christine Miller, previously of the PHLS, who stated: "Although the program will be aimed mainly at the **one to four** year age groups, where it will have the maximum effect, MMR vaccine can be given at any age." (Miller C. Introduction of measles/mumps/rubella vaccine. *Health Visitor* 1988;61:116-117)

Taylor et al noted that the rise in autism occurred in children born in the few years before 1987 and concluded, therefore, that since this rise had started before the introduction of MMR it could not have been caused by MMR. This paper has been cited by various vaccine officials as definitive proof of the safety of MMR in this context.

Taylor et al's omission of the crucial information on the catch-up campaign, led the reader to believe that those, and only those, born in 1987 were the first children eligible for MMR. They were challenged on this omission in a subsequent letter to the Lancet (1999;354). In their reply they acknowledged that they were aware of the catch-up campaign and admitted that no fewer than 36 autistic children in their data-set were born before 1987 and had, therefore, received their MMR over the age of 2 years. They claimed that this was not relevant since symptoms had apparently started in these children before MMR. This is not relevant; testing of a "step up" hypothesis is not based upon analysis of individual case notes, other than to confirm diagnosis. Since they were aware that their cohort contained children who received the MMR after the age of 2 years **it was not scientifically legitimate to test the hypothesis that a step up should be seen in those born in 1987**. The fact that the step up occurs in those born in 1986 is alarming, and would be consistent with an association with MMR.

Such were the anxieties about the quality of this study that it was recently the subject of a special, and highly critical debate at the *Royal Statistical Society* in London. The conclusion reached was that Taylor et al's study design was wrong.

Further evidence for a temporal association between the introduction of MMR and an increase in the numbers of cases of autism comes from a current study of autism in island populations. The data for Shetland are shown below.



Shetland Islands, Scotland.

A birth cohort effect for autism is seen in those born after the mid 1980's, corresponding with the introduction of MMR vaccine. Source Thrower D.

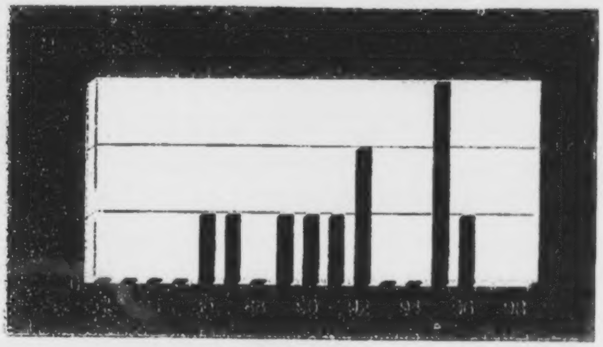


Figure . A similar birth cohort effect is seen for those born in the Western Isles of Scotland, a geographically distinct group from the Shetlands.

MMR and Compound effects

Parental reports have implicated the polyvalent MMR vaccine, but rarely the monovalent measles vaccine, in autistic regression. Is such a causal association consistent with what is known of the risks for acquired forms of this syndrome? Atypical patterns of exposure to common childhood infections - measles, mumps, rubella and chickenpox - have been associated with autism and autistic regression. *In utero* and infant exposures have been identified as periods of apparent susceptibility, when both the brain and the immune system are undergoing rapid development (Deykin EY and MacMahon B. *American Journal of Epidemiology* 1979;109:628-638). It is notable that a close temporal relationship in the exposure to two of these infections during the periods of susceptibility may compound both the risk and severity of autism. Although historically, these rare patterns of exposure may have accounted for only a small proportion of autism, the widespread use of a combination of the candidate agents in a single vaccine may have changed this. Recently, measles containing vaccines were linked to developmental regression (Weibel RE et al. *Paediatrics* 1998;101:383-387).

In order to understand why autsistic enterocolitis might result from a compound effect -- where the interaction of multiple concurrent viral exposures is important - it is helpful to examine the patterns of childhood infection that have been identified as risk factors for persistent measles virus infection and delayed disease. One important pattern of infection that may increase the risk of delayed disease is where different viruses interact, either with each other or both interact with the host immune system simultaneously. A close temporal exposure to measles virus and another infection, including chickenpox or an encephalitogenic enterovirus, is associated with an excess risk for a rare fatal encephalitis (subacute sclerosing panencephalitis), the onset of which may be delayed for many years. Similarly, atypical patterns of measles infection, including a close temporal exposure to mumps infection, but not other common childhood infections, have been identified as a significant risk factor for chronic intestinal inflammation - Crohn's disease and ulcerative colitis.

Clues that the component viruses of MMR could interfere, one with another, were provided in the very first pilot studies of this vaccine in 1969 (Buynak et al. *JAMA* 1969;207:2259-2262). However, despite providing compelling evidence of the potential for dose- and strain-dependent interactions between the component viruses in the MMR vaccine, both in the context of adverse reactions and antiviral immune responses, the matter was left in abeyance.

Six years later, in 1974, the potential for viral interference in MMR was the subject of a more detailed follow-up to the Buynak study, by Minekawa et al (*Biken Journal* 1974;17:161-167). The most striking observation was of a dose-dependent influence of the mumps vaccine upon not only clinical reactions to the measles component, but also seroconversion to rubella vaccine.

The ability of mumps virus to interfere with the cellular immune response to certain strains of measles virus and, thereby, in particular combinations potentially to reduce viral clearance and increase the risk of persistent infection, is an intriguing hypothesis to some of those involved in the current debate. Whatever the ultimate merits of this hypothesis, the contemporaneous interpretation of Minekawa et al was that further studies were necessary. However, it does not appear, from the published literature, that these further studies were undertaken.

Summary

- Autistic enterocolitis is a real syndrome
- The swollen intestinal lymphoid tissue provides a focus for searching for the cause(s) of this syndrome.
- The virological data indicate that this may be measles virus in some children.
- It would be imprudent to interpret the temporal relationship with MMR as coincidence, in the absence of thorough investigation.
- Epidemiologic and virologic data support the possibility of a compound effect of multiple concurrent viral exposures influencing: the clinical and immunologic response to MMR; the risk of autism; and, the risk of delayed sequelae, including chronic intestinal inflammation.
- Autistic enterocolitis appears to be important part of the current epidemic of autism and autistic spectrum disorders.

Conclusions

- If, following thorough independent scientific investigation, it emerges that autistic enterocolitis and other related disorders are causally related to a compound influence of the component viruses of MMR, whether these viruses have been encountered naturally or in the vaccine, then through judicious use of the vaccines, one may have a means for preventing the disease. Spacing the single vaccines, thereby dissociating the exposures that, together, may constitute the risk, provides a way of not only preventing the acute measles, mumps and rubella infections, but also, potentially, the risk of one of the most devastating diseases that it has been our misfortune to encounter.

Dr. O'LEARY. Mr. Chairman and members of the committee, the purpose of my testimony is to report the scientific results in a series of children with autistic enterocolitis that has just been described to you. Nothing in my testimony should or must be construed as anti-vaccine; rather, it encourages safe vaccination strategies. The opinions that I am expressing in the text and in my presentation are those of my own.

These studies were undertaken following an approach made to me by Dr. Andrew Wakefield, who has just submitted independent testimony. The studies represent a transnational, multidisciplinary research program aimed at elucidating the causes and pathogenesis of inflammatory bowel diseases in association with developmental disorders of childhood.

Next slide.

Dr. Wakefield has alluded to measles virus as a potential associated factor in the pathogenesis of autistic enterocolitis, and he came to our laboratory to seek molecular confirmation.

Next slide, please.

He posed some questions. The first question: Was measles virus present in gut biopsies from these children?

Next slide, please.

Where was it located? How much was there? Could it be sequenced—could we actually confirm there was measles virus? And finally, could different molecular technologies actually independently confirm the presence of measles virus?

May I inform you that I am a pathologist and a molecular biologist. My area of diagnostic expertise is histopathology, which is understanding and examining the cellular basis of disease.

Next slide, please.

The blinded study included 46 cases; 25 children had a diagnosis of autistic enterocolitis, and 21 controls were included in the study, including 15 normal children who did not have a developmental disorder, four children with Crohn's disease, which is a chronic inflammatory bowel disease condition, and two children with ulcerative colitis, a very similar condition but one which is histologically different.

We examined terminal ileal biopsies, and from the blocks of tissue that were given to us, we looked at four to six serial sections on the one case. What we wanted to do was to see if we could identify the virus; could we replicate it on multiple sections from one patient. Where available, fresh tissue was examined.

Next slide.

The positive control materials in this study were transvected measles virus-infected viral cells which contained measles virus genome, and measles virus-infected brain tissue. As negative controls, we screened a panel of other virally infected cells lines.

Next slide.

To confirm the presence of measles virus, we adopt a five-hit strategy. The first was to localize and identify the presence of measles virus RNA in the tissue sections from these patients.

The second was to quantify using a technology called TaqMan real-time quantitative PCR. I have worked in this technology for the last 6 years, and it is approximately 1,000 times more sensitive than existing PCR-based technologies.

Finally, we wanted to confirm the sequence of the virus, so we employed capillary fluorescent-based sequencing.

Next slide.

Let me summarize what in-cell PCR is. I know this is technical, but I think it is extremely important. Measles virus is an RNA virus, and RNA when it is removed from the body is extremely easily degradable. PCR basically is like a photocopying reaction. We can make multiple copies of a particular gene that we are interested in looking for.

In-cell PCR allows us to demonstrate these genetic sequences in cells and without cells, looking down the microscope.

Next slide.

TaqMan quantitative PCR basically is a revolutionary PCR-based technology which is sequence detection-specific. You will only get a positive result in this assay if the desired gene of interest that you are looking for is present in the tissue section.

Next slide.

In our laboratory, we are one of the few laboratories in the world that actually perform RNA inhibition assays. This is effectively to test how degraded the RNA in our samples is, and No. 2, is there anything in the environment of the laboratory that is contributing to the breakdown of RNA in tissue samples of cells.

Next slide.

I think it is extremely important in relation to the detection of low-copy viral infections, and I think our laboratory has a reputation for the detection of low-viral copy numbers, that we have strict anti-contamination measures. What I mean here is that we do not want to generate false-positive results.

So we have separate, isolated extraction and PCR areas. This is in a newly built, custom-designed molecular biology facility. We have two independent laboratory sites, and for the purpose of this investigation, we employed in situ hybridization, which is basically a way of taking a cloned or a fragment of DNA or RNA that you have in your laboratory and looking for the presence of that in a tissue section or cell. We can use the technology of in-cell PCR that I have described, solution phase PCR, and TaqMan PCR, which are complementary technologies, but TaqMan PCR is 1,000 times more sensitive than standard solution phase PCR technologies, and then sequencing.

Next slide, please.

Just to reiterate again the point: Our laboratories go to desperate lengths, No. 1, to prove that we do not have RNA inhibition, but second to prove that we do not have contamination. We purposely in all of our plates set up contamination. This is effectively to outrule the possible generation of false-positive results.

Again, I would appeal to the non-scientific members of the committee that this is an extremely important control that must be included if you are looking for low-copy viral gene detections.

Next slide, please.

And of course, to confirm the presence of measles virus, the gold standard is to confirm the sequence of the virus, to say yes, this is measles virus RNA that we have got in the tissue sections.

Next slide, please.

Let us look at the results now. We carry out an extensive set of optimization reactions where we had measles virus clones, looking at several regions of the measles virus genome, F, N, and H. The technical detail of this is not important, but just to show you that we could look at several genes within the measles virus genome, and we could reproducibly make copies of these or amplify them.

The bottom panel shows you an experiment which allows us to detect the measles virus in viral cells, showing what the optimal concentration of the probe that we require to detect the virus is, and you can see clearly that the optimum concentration is 1 to 1.5 micrograms per ml.

Next slide, please.

This slide shows the results of in-cell PCR by two different technologies. One is in-cell solution phase PCR, the other is in-cell TaqMan PCR, which produces a green signal in the right-hand panels, top and bottom. Again it demonstrates that we can clearly identify measles virus in these transvected cells.

Next slide, please.

This is a patient with subacute sclerosing panencephalitis. Measles virus is the cause of this condition. So of course, if we are to reliably detect measles virus in biopsies of the children that Dr. Wakefield provided to us, we should of course be able to identify measles virus in brain biopsies from patients with SSPE.

The left panel and the middle panel show measles virus presence in these biopsies, and the right-hand panel is the negative control.

Next slide, please.

This is a case of an autistic child No. 1. You can see the top left-hand panel is a microscopic appearance of what the gut looks like—and this is not normal gut epithelium from a child; it is heavily inflamed. The bottom left-hand panel show a spidery, black deposit, outer width of the cells that are in green. This is actually measles virus RNA. The top right-hand panel again in a different field shows a heavier deposit of black, which again is measles virus, and again, I need to point out to you that this is outer width of the cells that are surrounding it.

Measles virus was located in the tonsils, in the lymphoid hyperplastic areas that Dr. Wakefield described on endoscopy. And the negative control is absolutely clean.

Next slide, please.

This is another case, a second autistic child, again showing a very similar findings—a black deposit, which is measles virus, outside of inflammatory cells, associating the fibrillary matrix, and the negative controls here for mumps are absolutely clean.

Next slide, please.

I think this slide is extremely important. If you look at the left-hand panel, this is measles virus for the nucleocapsid gene. It is a black signal. It again is the outer width of the cells, but it has a spidery, cobwebby morphology. There are little processes and tentacles coming out of this region. If you look at the top right-hand panel, the follicular dendritic cell has processes, dendrites, which form the cell matrix, which is very, very similar to what we see on the left-hand panel. And the immunocytic chemical staining analysis which Dr. Wakefield alluded to gives exactly the same results.

Next slide, please.

By solution phase PCR, by what we call fairly standard laboratory protocols, we can detect the measles virus in gut biopsies from these children, and the negative controls are appropriately negative.

Next slide, please.

Even in a paraffin-embedded tissue section that has probably been sitting around in wax for 4 to 5 years, we can detect measles virus. That is an astounding finding in view of the fact that wax and fixation by itself breaks down RNA. This graph shows in real time, we can look at the accumulation of the PCR product that we are making, confirming that measles virus is actually present in this biopsy.

Next slide.

And of course, we can sequence it, and we can say that this is measles virus RNA present in the biopsies of these children.

To do this properly, you need to do it in a forward and negative strand. I started off by saying that measles virus is an RNA virus. When we make copies of the RNA virus, we make copies in two-strand forms. So if we are to sequence it, we should sequence in a forward and reverse strand.

Looking at that electrophoretogram, the sequences in both directions are exactly the same.

Next slide, please.

In summary, then, in terms of the association that Andrew Wakefield alluded to, I can confirm that his hypothesis is correct—24 out of 25 children—that is 96 percent of the children's biopsies that he sent to my laboratory, blinded—children with autistic enterocolitis harbor measles virus genomes.

Three out of four patients with Crohn's disease—these are children with Crohn's disease—and one out of two children with ulcerative colitis also contain measles virus. That is an interesting biological fact.

Finally, 1 of 15, 6.6 percent, of control children harbored measles virus genome. I think it does not take greater statistical analysis to work out that there is a significant difference between 24 out of 25 and 1 out of 15.

Next slide.

Solution phase RT-PCR, which is standard laboratory-based technology, was positive in all children with autistic enterocolitis for different regions of the measles virus genome. That is extremely important. And we can sequence measles virus isolates from these children.

Final slide, please.

However, the infection that is present in these children is at extremely low copy, at about 5 to 30 transcripts per approximately 2,000 cells.

Now, again, I want to add some technical overlay on this. The way that we quantify RNA in our laboratory is by a method called copy RNA. Again, we are one of the few laboratories worldwide that would do this as the most accurate way of actually measuring RNA. Indeed, industry now is accepting this as a standard way of quantifying RNA in cells of tissue sections.

Finally, the presence of measles virus was identified by in situ hybridization, by solution phase PCR, by TaqMan PCR, by in-cell

PCR, by sequencing. This really, in terms of technology, is as good as it gets right now.

I hope that I have given you evidence here which is compelling in relation to the presence of measles virus in children with autistic enterocolitis.

Thank you for your time and attention.

Mr. BURTON. Thank you, Professor, and when we get to the question-and-answer phase, I am sure that we will try to ask questions in layman's terms and try to get some answers so that we can understand everything that both you and Dr. Wakefield said—but I think we got the gist of it.

Dr. Singh.

[The prepared statement of Dr. O'Leary follows:]

Testimony before Congressional Oversight Committee on Autism and Immunisation by John J. O'Leary MD, PhD, MSc, MRCPath.

Mr. Chairman and members of the committee,

The purpose of this testimony is to report the scientific results in a series of children with autistic enterocolitis. Nothing in this testimony should be construed as anti-vaccine, rather it encourages safe vaccination strategies. The opinions expressed in this text and attendant presentation represent those of the author, and are not representative of any organisation or institution.

The studies were undertaken following an approach made to me by Dr. Andrew Wakefield (who has submitted independent testimony). The studies represent a trans-national, multi-disciplinary research programme aimed at elucidating the causes and pathogenesis of inflammatory bowel diseases and developmental disorders of childhood.

Biopsy material for this study was provided by Dr. Wakefield and presented to my laboratory using "blinded protocols". Unique accession numbers were then assigned to each case to maintain patient and diagnostic anonymity. Senior scientists and technicians have carried out the research work at a dedicated state of the art molecular biology facility.

Dr. Wakefield posed three questions to our group in relation to autistic enterocolitis:

- Was measles virus present in gut biopsies of affected children?
- Where was measles virus located in gut biopsies of affected children?
- How much virus was present in gut biopsies of affected children?

Following scientific discussions it was decided to augment this panel of questions by including two additional important questions:

- Could measles virus genomes be sequenced from gut biopsies from children with autistic enterocolitis?
- Could different molecular technologies be employed to confirm the detection of measles virus genomes in affected children?

Before commencement of the project a standard operating procedure (SOP) was written in relation to handling of samples, extraction of nucleic acid and performance of molecular virology screening assays. The assays used in this study were:

- In-situ hybridisation (with and without tyramide signal amplification [TSA]).
- In-cell PCR
- Solution phase PCR
- TaqMan quantitative PCR
- DNA sequencing

Specific regions of the measles RNA genome were selected as detection targets. These included the haemagglutinin (H), nucleocapsid (N) and fusion (F) regions of the measles genome.

Strict anti-contamination procedures were adopted throughout the study to prevent false positive results being generated. These included separate and isolated facilities for nucleic acid extraction, PCR amplification, in-situ hybridisation and DNA sequencing.

TECHNOLOGIES:

In-situ hybridisation:

This technique allows localisation and visualisation of genetic sequences (DNA and RNA) in cells and tissue sections. The in-situ hybridisation assays employed cloned cDNA (copy DNA) fragments of the H, N and F region of the measles genome. Cloned fragments were labelled with biotin and /or digoxigenin using standard nick translation technology. Hybridisation (specific attachment) of probe to the target sequence in cells and tissues was carried out using conventional chemistries. Detection of the formed hybrid was achieved using standard immunocytochemical techniques. In all cases tyramide signal amplification (TSA) was applied to increase detection sensitivity.

One-step immunocytochemical detection has a sensitivity of 50 genome copies per cell; three step immunocytochemical detection has a sensitivity of 10 – 15 copies per cell: However, TSA achieves single copy viral gene detection in cells and tissue sections.

In-situ hybridisation assays were performed on serial sections of gut biopsies from affected children. Hybridisation efficiency was assessed using a conserved human repeat sequence (i.e. present in every cell). Negative control probes included Human Papilloma virus types 16 and 18 and Human Herpes Virus 8.

Immunocytochemical and detection controls were included in all assays.

Optimisation experiments were carried out using measles virus infected Vero cells and brain biopsy material from patients affected with sub-acute sclerosing pan-encephalitis (SSPE), which is caused by measles virus.

In-cell PCR:

This technique allows the investigator to amplify (make copies of) DNA and RNA in cells and tissue sections with a detection sensitivity of one viral or mammalian genome copy per cell. The location of the virus within the tissue can be identified. In addition, problems with DNA and RNA contamination are not encountered using this method, because only DNA/RNA present in tissue sections (i.e. either inside or outside cells) will be amplified and localised. (Figure 1).

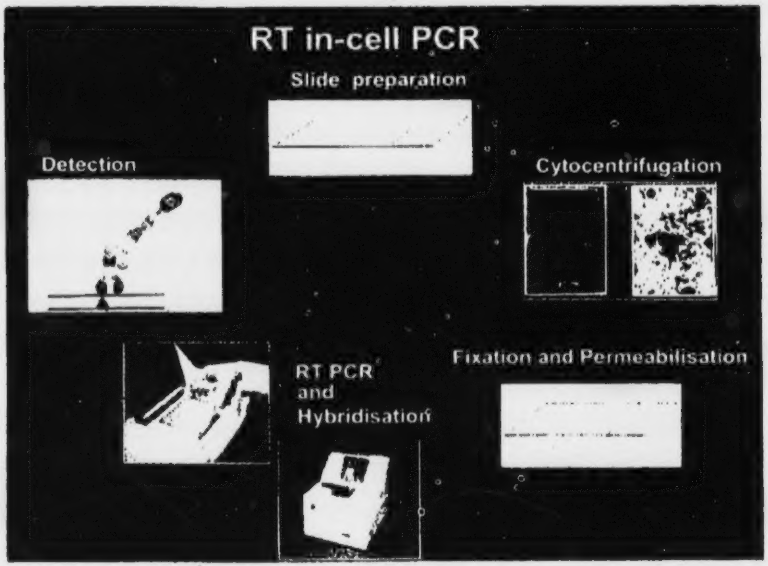


Figure 1: Schematic representation of RT in-cell PCR

In these cases, measles virus RNA was amplified using in-cell RT-PCR (reverse transcriptase PCR). This technology employs a polymerase chain reaction (PCR) step (in order to make copies of the RNA molecule) and a hybridisation step using a labelled probe to detect the newly formed amplicon (gene copies).

Optimisation experiments were carried out using measles virus infected Vero cells and measles-infected brain biopsy material from patients with sub-acute sclerosing pan-encephalitis (SSPE).

Four to six serial sections of gut biopsies from affected children were examined for the presence of measles virus, while including appropriate controls, i.e.

- omission of reverse transcriptase enzyme,
- omission of DNA polymerase,

- using irrelevant primers
- immunocytochemical and detection controls.

Solution phase PCR:

For affected children from whom frozen biopsy material was available, solution phase PCR using primers to H, N, and F regions of the measles virus genome was performed. (Figure 2).

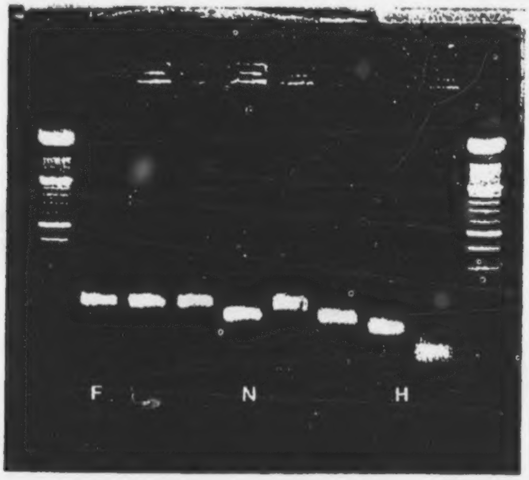


Figure 2 **Solution phase PCR of F,N and H genes of measles virus.**

Optimisation experiments were carried out using measles virus infected Vero cells and brain biopsy material from patients affected with sub-acute sclerosing pan-encephalitis (SSPE), which is caused by measles virus.

The detection sensitivity of single round PCR is 15 viral copy RNA equivalents (cRNA) in 10^5 RNA sequences.

Taq Man quantitative PCR:

This technique allows automated quantitative PCR analysis of RNA and DNA gene sequences. My laboratory has been involved with this technology for approximately 5–6 years. TaqMan PCR utilises two primers (as in conventional

solution phase PCR), but in addition uses a probe labelled at one end with a fluorescent reporter molecule and at the other end by a fluorescent quencher molecule. These molecules are chosen so that the reporter emits fluorescence at the specific wavelength that the quencher will absorb fluorescent light. No fluorescence can be detected when the probe is intact due to the proximity of the reporter molecule to the quencher. The probe is designed so it will bind to the target sequence between the two primers.
It is also important to note that TaqMan PCR utilises a characteristic of the enzyme Taq polymerase, namely its 5' nuclease activity.

If the target sequence of interest is present, then both primers anneal (stick) to the ends of the target sequence. At the same time hybridisation (sticking) of the TaqMan probe occurs. During the extension phase of PCR, the TaqMan probe is displaced and cleaved (broken) with release of the reporter molecule into solution away from the quencher sequence. For each new copy of the gene that is made, one reporter molecule is released which can be monitored in a specifically designed sequence detector (7700 sequence detector (PE Biosystems)).

The assay is entirely sequence specific and does not yield false positive results. In addition, it is a closed tube assay, which minimises potential contamination events. (Figure 3).

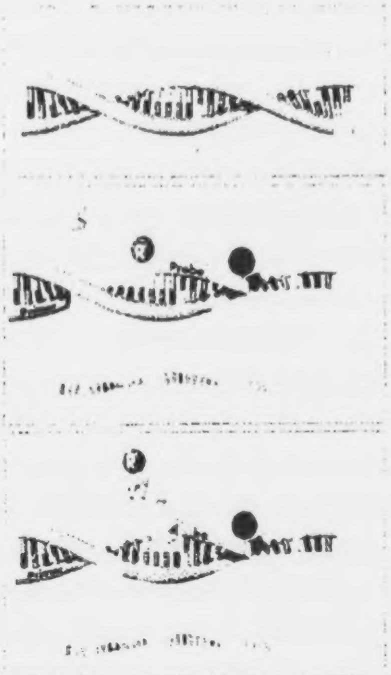


Figure 3 **Schematic representation of TaqMan PCR**

DNA sequencing:

Sequence confirmation of measles virus genomes was carried out using the ABI Prism 310 capillary sequencer (PE Biosystems). BigDye terminator chemistry and cycle sequencing was employed to validate derived sequences. Positive and negative strand sequencing was performed with subsequent alignment of genetic sequences using BLAST search software. (Figure 4).

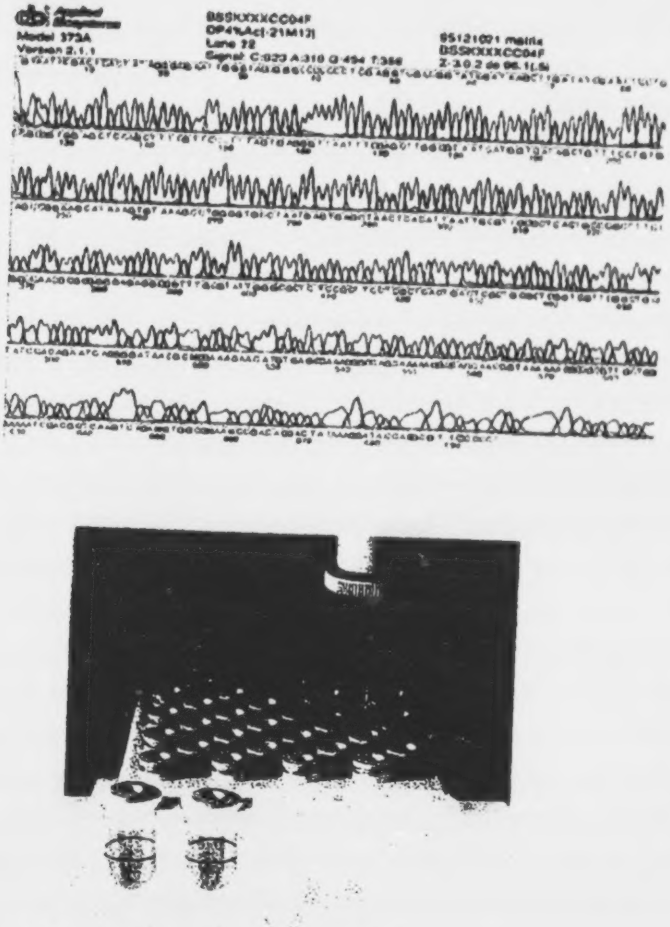


Figure 4. Electropherogram readout of a sequencing reaction. Bottom plate illustrates capillary 310 platform.

RESULTS:

I. Optimisation experiments

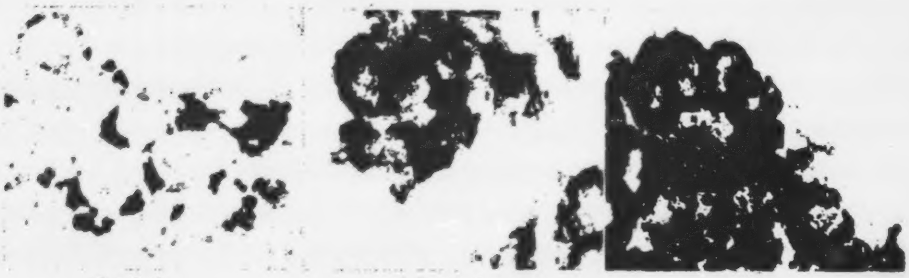


Figure 5 (above) demonstrates the optimisation experiments for RT-in-cell-PCR assays with measles virus transfected Vero cells. Copies of measles virus RNA can be seen in the cytoplasm of the cells. The intensity of the signal is dependent on the concentration of probe used for the hybridisation component of the assay.

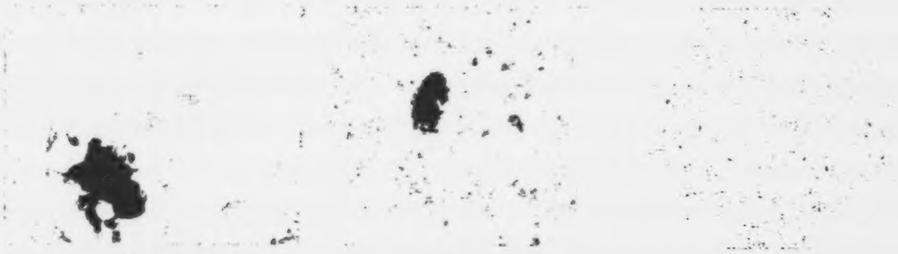


Figure 6 (above) demonstrates in-cell PCR results in patients with SSPE. Note the presence of measles virus genomes in brain tissue of affected patients.

140

II Biopsy results

Using RT in-cell PCR and in-situ hybridisation with TSA, we are able to identify measles virus genomes in follicle centres of lymphoid aggregates of gut biopsies from children with autistic enterocolitis. The signals obtained (see Figure 7) appear to be extra cellular and fibrillary in nature. Localisation of measles virus genomes was confirmed on serial sections from the same patient. In each biopsy, 1–3 loci of amplification were identified; indicating low measles virus copy number. The results must be taken in the context of formalin fixation, which, by its nature degrades RNA molecules in cells and tissue sections.

The fibrillary pattern seen by in-cell PCR is similar to immunocytochemical results obtained for measles virus N-protein immunocytochemistry (see Figure 7).

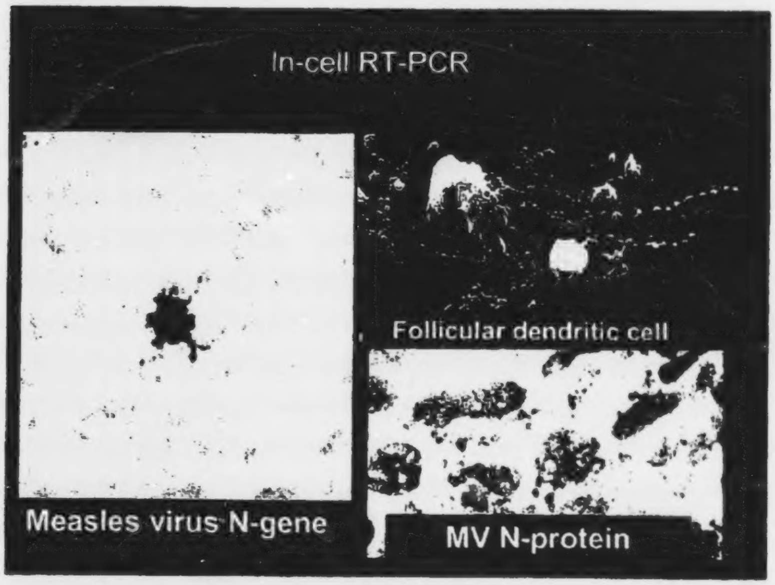


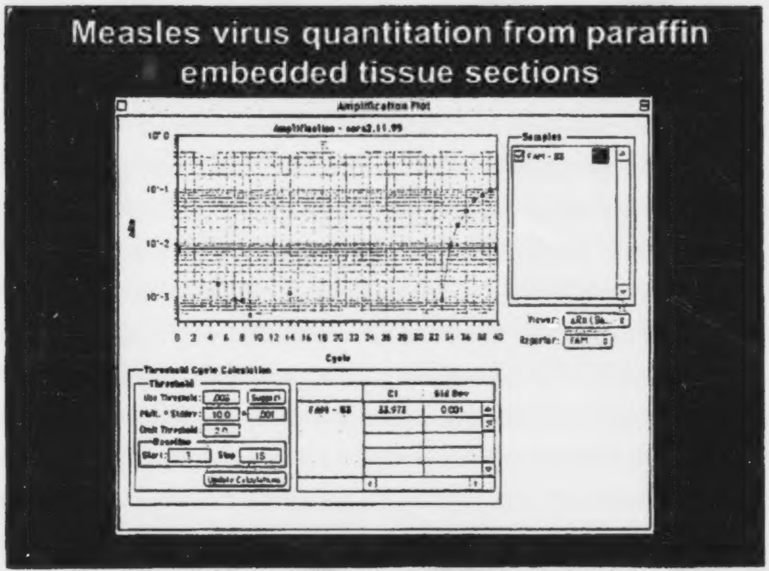
Figure 7 **Left panel illustrating RT in-cell PCR results. Note the fibrillary quality of the signal, which is extracellular.**
Top right panel: published electron microscopic image of a dendritic cell showing fibrillary processes of the dendritic cell matrix.
Bottom right panel demonstrating measles virus N-protein in a follicle centre. Brown/orange stain indicates positivity.

Measles virus genomes were identifiable by standard solution phase PCR (see Figure 8) using fresh frozen gut biopsies from children with autistic enterocolitis.

1: Patient 2:MV-F-protein (150bp)
2: Patient 3:MV-F-protein (150bp)
3: Patient 2 :MV-H-protein (150bp)
4: Patient 3: MV-H-protein (150bp)
5: pos.control:MV-H-protein
6: pos.control:MV-F-protein
7: pos.PCR control (PDH Junc)
8: neg.control

Figure 8 Measles virus – solution phase PCR of patient samples.

Using TaqMan PCR, we have been able to quantify the measles virus copy number per 1,000 mucosal cells using 'gene dosage correction formulations'. The copy number of measles virus in gut biopsies from children with autistic enterocolitis is low, at approximately 30 – 50 measles virus genomes per 2,000 mucosal cells (including gut epithelial, lymphoid and dendritic cells) (Figure 9).



Measles virus quantitation from paraffin embedded tissue sections

Amplification Plot
Samples
10^0
10^-1
10^-2
10^-3
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40
Cycle
Threshold Cycle Calculation
Threshold
Baseline
Ct
Std Dev
Update Calculations

Figure 9 TaqMan PCR amplification plot of a measles virus amplicon from a paraffin embedded tissue section of an affected child.

Confirmation of the presence of measles virus genomes was achieved using positive and negative strand sequencing of cDNA measles amplicons (see Figure 10).

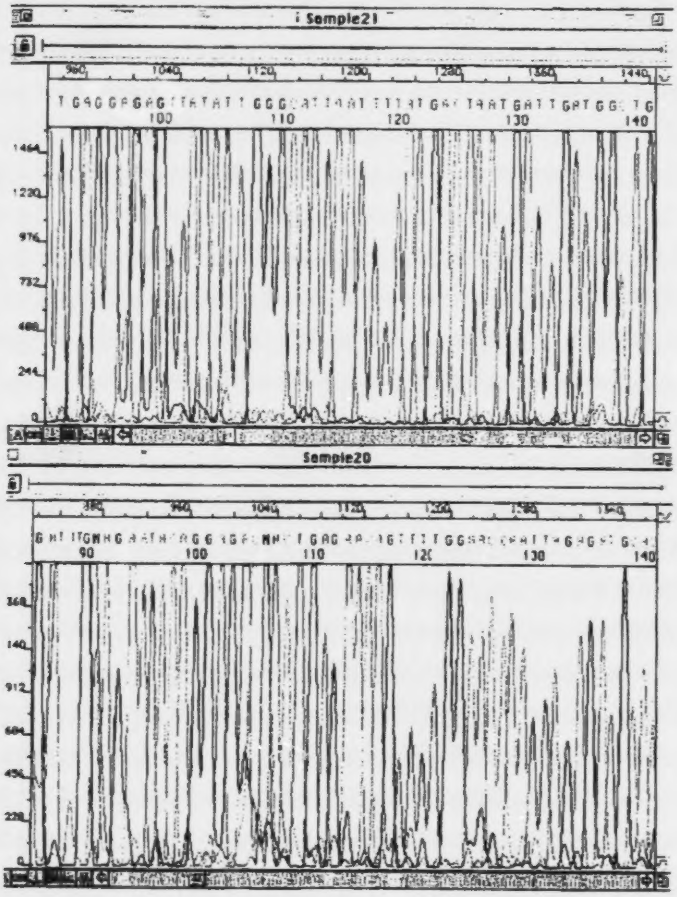


Figure 10 **Positive and negative strand sequencing of measles virus F region in an affected child.**

Mr. SINGH. Thank you very much, Mr. Chairman.

I did not realize that I could have shown a couple of slides as well to make the point much more in layman's language, but I will try to explain the results of the research that I am involved in.

It has been nearly 25 years that I have been involved in so-called childhood diseases, from the immunology side as well as the pediatric neurology side. I was working at Children's Hospital in Vancouver, Canada, which is where I began my career in childhood diseases, and early on, I saw a few examples of autism mentioned in congenital rubella syndrome. It was a fascinating observation, because at that time, I was very excited about the research on virus infections and nervous system disorders. That really led me to kind of work back and forth between nervous system disorders and virus infections and immunology.

So the whole thing here is that we need to consider combination of these disciplines that we talk about. We are not going to be able to answer any questions as far as I am concerned about nervous system diseases simply by studying psychology or simply by looking at the epidemiology data. We need to come together as a team to focus histories of nervous system, immune system, and whatever else comes into the picture. That is one major focus of attention that at least I am taking for my future research.

On autism as an immune disorder, I think I am probably one of the earlier investigators who started working on the immunity and autism connection. Followed by that was my theory that autoimmunity is a very important process in autism. That is partly because I was studying autoimmunity in nervous system disorders like multiple sclerosis and Alzheimer's disease. Quite frankly, some of my earlier work in Alzheimer's disease has opened the way, and today, people are actually using immunology as a platform to design treatment for Alzheimer's disease.

It was funny to see on the news last night that some doctor has a new approach; he says he is going to use immunology as a means of activating the nervous system in order to correct the Alzheimer's problem. That is a fascinating stuff, at least to me.

So I started to pay more and more attention to autism, and the results that I am going to share with you are actually quite unique to autism. They are part of the nervous system, but they are being analyzed by the immune system research.

I know there are people, especially who are funded by NIH or by CDC, who continue to make no mention at all of this so-called immunology research or autoimmunity research in autism. I have been invited by the NIH panel; I have made two trips to NIH panels. I made a visit to the Institute of Medicine and the National Academy of Sciences about 1½ or 2 years ago. And if you hear those people who have been funded by these agencies, when they go out and present, they do not even mention anything about autoimmunity in autism. NIH people prepared a document of that meeting. It was designed for updating the screening and diagnostic criteria. If you read that document, there is virtually no mention of this sort of research. To me, this is simply mind-boggling.

Is it because people out there in the scientific community do not want to buy the argument, or are they just being naive about what is already coming out in the way of solid, decent, experimentally proven research?

Now, having given that background, let me show you some of the results. First of all, I started looking at autism as an autoimmune disorder, as I mentioned. And what we have found is over the last 5 or 6 years of research—and I think now, the number of cases I have studied is approaching about 400 cases—very early on, I wanted to study the myelination problem in the brain. You will ask what is myelination. It is one of the most critical events in the nervous system development. So when a child is actually growing, this myelination process is very important. It is really more or less like a mother will feed a child and perhaps nurse in such a way that this process has to be nurtured very, very carefully.

Having said that, what we are finding is auto-antibodies. Auto-antibodies are the hallmark of the autoimmune process. If you have an autoimmune process, you are going to have auto-antibodies, but if you have those antibodies against an organ which is affected in a disease—in autism, what would that be—that would be the brain. So we are finding brain auto-antibodies in autobodies.

What I am trying to illustrate in this chart is that we had a number of normal children, normal adults, patients with other disorders, Down syndrome, and none of those seemed to show these auto-antibodies, but on a rare occasion, 1 or 2 percent positive in the normal or control population.

Here, we have a scientific observation which anybody can go out there and repeat. I do not think I need to use any difficult thing to illustrate that point. It is a consistently reproducible result, and it is happening now in children all over the world. I am getting specimens from overseas as well, not just the nationwide specimens alone. So this is a very important thing.

Furthermore, I find that particular protein marker is selective, because I have now studied two additional markers of the same structure in the brain, and I do not find these auto-antibodies in autism.

Let me move on to the next issue. What happens is, assuming there is an autoimmune process, most autoimmune diseases are triggered by virus infections. So I started to think about looking at viruses. I was not thinking of the vaccine issue at all. I was thinking of virus infection. And, quite surprisingly, when I started to do antibody measurements to viruses which are out there or temporarily associated, what I found was that the measles virus stands out as statistically significant in terms of its antibodies, significantly much higher in autistic children. So these children have what is so-called hyperimmune response to the measles virus—not other viruses. We studied rubella virus, HHV–6 virus, cytomegalovirus, and none of those three viruses showed this hyperimmune antibody response.

Furthermore, the important thing is the measles antibodies which we have now measured by two different methods, and the result is the same—a statistically significant increase.

The next thing I wanted to see was if anything correlated between these two parameters. Quite strongly, I found that brain auto-antibody-positive patients also had measles antibody levels which were very high. So the higher the antibody level to measles virus, the higher the chance of brain auto-antibody. It does not take too much intelligence to make some sense here now.

Over the years, some of these families have been sending me written notes or telephone calls and so on, and every time I was going out to make my presentation, people would tell me about the vaccine connection with autism.

Early on, I was not sure what was happening. So I tried to put together their own reports, and the report looks like this in the pie chart. Nearly 53 percent of the families reported that their child got autism because of MMR. The remaining 30 percent said it was because of the DPT shot. And about 15 percent—this was a critical category for two reasons—about 7 percent said they were not sure whether it was measles or DPT, but the remaining 7 percent had no history of vaccination connection, or at least they did not make the connection. I wonder if that 7 or 8 percent category is where Dr. Dankner's child might fit in.

The last point I want to make is that of a very recent research finding of my own, not yet published, but something quite important. About which I showed a slide in my presentation in a meeting last year which was held in Orlando, FL. This is an observation of antibodies to measles, mumps, rubella (MMR) itself. I decided to start with measles, mumps, rubella, because that is the largest population which was reported to me as being affected by the measles vaccine.

We took the vaccine preparation itself, and we decided to examine antibodies in these children. Normal children do not show any antibody to a protein that I will point out in a second, but in children with autism, nearly 65 percent of them showed that antibody.

Actually, I can illustrate that point a little more if we just imagine that I am a molecule, or a preparation of measles, mumps, rubella. This protein, this antibody that I am detecting will be something like detecting this coat pin. In other words, antibodies to this protein which is present in the measles, mumps, rubella vaccine preparation were found in autistic children, but not in the normal children. I think this is a very, very important laboratory-based research evidence. If anybody wants to make a criticism of that, of course, they are at liberty to do so. However, I find this is a scientifically very, very important observation, telling us that perhaps there is a good connection, there is something happening with this measles, mumps, rubella vaccine in these children, something is unusual.

So basically, after having illustrated some of these points, I want to make a final comment. That is, if you really look at the literature reported on the vaccine adverse reactions, I do not think you will need a crystal ball to see that vaccines have adverse reactions. The literature is full of those reports. What is not there or is it has never been reported, or at least, the officials from the CDC continue not to mention anything about it. What they mention is that vaccines are good. Every week, you read about it in the newspaper, and you hear about it on the television. And I do not dispute that information because I know vaccines are very, very important. My concern as a researcher now, more so than ever before, is that we must pay attention to the safety of these vaccines. It is missing; it has not been disclosed publicly, and I do not think it exists in the literature, and therefore, I urge the Government Reform Committee to look into particular new policies concerning the vaccine safety issue.

Thank you very much.

Mr. BURTON. Thank you, Dr. Singh.

Dr. Boyle.

[The prepared statement of Mr. Singh follows:]

Vaccines-induced Autoimmunity in Autism

By

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Today, I will be speaking about the autoimmunity aspect of vaccines in autism, a medical condition that has been largely ignored by the medical community and federal government for a very long time and yet the incidence of autism is increasing at an alarming rate. An estimated one-half of a million Americans, mainly children, and millions more worldwide are known to suffer from autism, a heart-rending disorder that severely impairs higher brain functions: social interaction, communication, language, imagination and cognition. The disorder is a life-long mental disability with devastating consequences for both the patient and his/her family. Thus the financial burden is huge for the families who care for children with autism.

Autism is an idiopathic brain disorder, which simply means that the etiology of the disorder is not known. And there is no single, clear-cut cause for autism. **Causally speaking, I tend to think that autism is a complex disorder, in which autoimmunity to brain plays a key role. Today, in spite of virtually no funding available, autoimmunity is the most extensively investigated topic of research in autism.** This is by and large due to the fact that autoimmunity is the prime target of therapy that has proven to be quite effective in ameliorating autistic characteristics. Thus the autoimmunity research, unlike the genetic research, has already significantly improved the health and welfare of individuals with autistic disorder. I have recently coined a term "Autoimmune Autism (AA)" to refer to a subset of autism that has autoimmune etiology. Moreover, there are scientific reasons to think that this subset may indeed be a result of vaccine injuries to children who display autistic regression.

Autoimmunity is an abnormal reaction immune reaction, in which the immune system becomes primed to react against body organs. It's a mosaic of highly complicated interactions and networking between cells and molecules of the immune system. The body makes autoantibodies against itself, resulting in damage to tissues and organs. The "autoimmune" response is what happens in autoimmune diseases such as lupus, and my research showed that a similar response my account for the brain abnormalities found in people with autism.

Autoimmune diseases are identified and characterized by many factors. The hallmark is the "organ-specific autoantibodies" that have also been identified in people with autistic disorder. To that end, I have recently summarized laboratory data of approximately 400 cases (autistic and controls) and found that up to 80% of autistic children have autoantibodies to specific brain structures, in particular a brain protein known as myelin basic protein (MBP) of the myelin sheath, a fatty coating that insulates nerve fibers and absolutely essential for higher brain functions. These autoantibodies are present quite frequently (65-85%) in autistic children, but only rarely (0-5%) in normal children and other disease controls. Accordingly, I postulated that autism involves a specific autoimmune response to MBP -- an immune assault that impairs myelin development in the developing brain, thereby modifying the nerve cell functions of the brain. Ultimately, by way of impaired wiring diagram in the brain, this results into autism.

Autoimmunity is commonly triggered by environmental exposures such as viral infections. Virus serology (or virus antibodies) is an excellent tool for studying virus infections in disease states. However, until recently, such studies had not been performed for autism. Because of my ongoing research, I became interested in examining a virus link with autoimmunity in autism. I recently raised two specific questions: (1) Does autistic children have a hyperimmune response (or increase of antibodies) for a specific virus? (2) Is there a relationship between virus antibodies and brain autoantibodies in autism? I conducted a carefully designed study to address these two questions. Succinctly, I made two very important observations: first, there was indeed a hyperimmune response to a virus and it was specifically for the measles virus (MV), but not for the other viruses tested [human herpesvirus-6 (HHV-6), rubella virus (RV), and cytomegalovirus (CMV)]; and secondly, there was an association between measles virus antibodies and MBP autoantibodies (i.e., the higher the measles virus antibody level the greater the chance of brain autoantibody). Few months earlier in the same year (February, 1998), I had already found that many autistic children had antibodies to a specific protein of the measles-mumps-rubella (MMR) vaccine (MMR vaccine preparation). These viral antibodies were also related to positive titers of brain MBP autoantibodies. **This was most probably the first laboratory-based evidence to link measles virus and/or MMR vaccine to autoimmunity in children with autism. Collectively, these observations led me to speculate that autism may be caused by a measles- or MMR vaccine-induced autoimmune response.** Unfortunately, due to lack of funding, I have not been able to extend this research and the progress has been hampered.

As I made scientific presentation of my initial findings, a vaccine-autism connection became even more apparent. I compiled a nonscientific, anecdotal survey of vaccine-injured children with "autistic regression" or autistic disorder, as reported by families. *Surprisingly, up to 93% of the reported cases had autistic symptoms shortly after vaccinations (52% post-MMR, 33% post-DPT, and 8% post-MMR and/or post-DPT).* The remaining 7% of the reported cases were not linked to any vaccination at all. Indeed, if these numbers are reproducible, **the data will lead to inescapable conclusion that these vaccines can potentially cause autoimmunity in autism.** Quite candidly, this will not be first time that a vaccine has been linked to a disease or disorder. There is quite a bit of literature linking vaccines to autoimmune diseases. Furthermore, an epidemiological study just published in JAMA (March 8th issue) described "extraimmunization" amongst American children and considered it to be a contributing factor for the adverse effects of the vaccines. And I think the vaccines and autism connection is no exception to these adverse effects.

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In summary, the rapidly accumulating evidence strongly implicates autoimmunity in autism, which in many may result from a vaccine injury. There is a possibility of an atypical measles infection in autism, but the evidence also suggests a MMR vaccine infection. Without any reservation, I would strongly recommend that this Congressional Committee reviews all the information in bipartisanship, and **explore the possibility that drug companies never properly evaluated the safety of vaccines in the first place**. If this indeed were true then it becomes imperative that we as a society must pay an immediate attention to this problem; otherwise, an epidemic of autism is a real good possibility. There should be no mistaking about it because autism is on a sharp rise and vaccinations, especially the extraimmunization, could potentially explain this rise. **The onset of autism (or autistic regression) post-immunization should no longer be regarded as merely a coincidence with the timing of the vaccinations, as our federal health officials continue to do. We must find new ways to curve adverse effects of vaccines, including autism.** Considering a population of 500,000 cases of autism in the United States, the autoimmunity research, but not the genetic research, has already had a great impact on the health and welfare of autistic people. Since brain autoimmunity is found in up to 85% of cases, it can potentially help an estimated 425,000 Americans. Indeed, many of them are already reaping the benefits of the experimental autoimmune therapy. Thus there is an urgent need to promote autoimmunity research in autism. This recommendation is in contrast to the opinions held by the directors of the federal agencies and major private foundations (Cure Autism Now and National Alliance for Autism Research) who are erroneously committed themselves to fund genetic research only. Finally, I urge the Government Reform Committee to provide leadership for new solutions to the existing problems surrounding autism research, and request the Committee Members to be visionary and offer new hope to the people with autism -- The essence of life is to care.

Ms. BOYLE. Good afternoon, Mr. Chairman and members of the committee. I am Dr. Coleen Boyle, Chief of the Developmental Disabilities Branch at the Centers for Disease Control and Prevention. I am presenting the agency's testimony, and I am accompanied by Dr. Ben Schwartz, who is the Acting Director of the Epidemiology and Surveillance Division at the National Immunization Program at CDC.

I am pleased to discuss our work at CDC to prevent developmental disabilities including autism. I want to begin by assuring the parents that we have heard from today that CDC is concerned about autism, and that we are working hard to find the causes of autism and other developmental disabilities so that all children will have the opportunity to have a healthy and productive future.

Autism is a serious developmental disability which can have profound impact on children and their families. It is characterized by qualitative impairments in social interactions and communication and a pattern of restrictive, repetitive, and stereotypic behaviors, interests, and activities. Autism may require long-term special education and care at a cost of more than $30,000 per year. Costs for residential care can be $80,000 to $100,000 per year.

CDC's role in preventing developmental disabilities including autism is to track the disease rates in the population and to identify causes of this condition. CDC can then establish prevention programs and then evaluate how well these programs work.

We do not know if autism rates are going up. Early studies found autism rates in the range of 4 to 6 per 10,000 children, using a narrow set of criteria. More recent studies have reported rates averaging 12 per 10,000 children, but these studies have used different criteria than the earlier studies.

CDC is not certain how much of the reported increase is due to changes in the definition of autism or an improved recognition of this condition over time. We also do not know if other factors have contributed to the larger numbers of children seeking treatment.

CDC is currently developing ways to better measure autism. In 1998, we added autism to our Metropolitan Atlanta Development Disabilities Surveillance Program. This program, which also monitors other serious developmental disabilities such as mental retardation and cerebral palsy among school-age children in Atlanta, is the only community-wide study in the United States. CDC has just funded Marshall University in West Virginia to start tracking autism in six countries in that State.

At this point, I want to briefly describe our activities in Brick Township, NJ and in investigating the alleged association between autism and the MMR vaccination.

In early 1998, the CDC and the Agency for Toxic Substances and Disease Registry [ATSDR], were contacted by the New Jersey Health Department, Senator Robert Torricelli, and U.S. Representative Christopher Smith, requesting the CDC investigate autism rates in Brick Township. They were concerned that the number of children with autism was too high.

In response, CDC conducted a study of children with autism living in Brick Township during 1998. ATSDR investigated sources of environmental pollution and exposure routes in Brick Township. All the data have been collected, and the results are currently undergoing scientific review. Once this review is completed, we will provide the report first to the parents of the affected children, the community, and then the local and State health departments. We would be pleased to brief interested Members or their staffs on the results of this work at the time we make them available to the community.

As the committee is aware, a theory links the MMR vaccine and autism, which has generated public interest and some controversy. CDC believes that the current scientific evidence does not support the hypothesis that MMR or any combination of vaccines cause the development of autism. Initial case series reports have not been substantiated by more focused reviews or by more in-depth follow-up research.

It should be pointed out that factors known to be associated with autism include genetic factors and events that occur before birth.

CDC recognizes how important it is to identify the causes of autism as well as to ensure the safety of vaccines. CDC is currently undertaking three studies related to autism or about hypotheses related to vaccines and autism.

First, CDC is using its Autism Surveillance Program in Atlanta to examine the possibility of a link between the MMR vaccine and autism.

Second, we are working with the National Institutes of Health to conduct a study that will evaluate whether vaccination is linked with developmental regression which occurs in some children with autism.

Third, CDC is using the Vaccine Safety Datalink, in collaboration with several HMOs, to study inflammatory bowel disease and the MMR vaccination.

Through these studies, CDC is working to assure the safety of the vaccination program and to identify preventable causes of autism.

Mr. Chairman, in the past 4 years, public health has made significant advances in preventing developmental disabilities. Prevention of congenital syphilis and congenital rubella syndrome have spared lives and prevented disability for thousands of children. Newborn screening programs have prevented lifelong mental retardation in children with hyperthyroidism and sickle cell disease.

However, given these strides, we still do not know what causes many developmental disabilities, including autism. While additional scientific research is being completed, it is important to also consider the broader context of public health, including the vaccination program, which is one of the most successful public health achievements of the 20th century.

Given the weight of the scientific data and the known seriousness and ongoing risk of vaccine-preventable diseases, in CDC's judgment, the best public policy is to continue vaccination unchanged while aggressively working to try to identify causes of developmental disabilities.

CDC agrees with the committee and the parents who have testified today that autism has a significant and profound adverse impact on the lives of children and families and communities where it occurs. We must track this disorder, we must identify the preventable causes, and we must institute effective prevention programs.

It is my hope that our efforts, combined with those of the NIH and the academic community, will lead to a way to prevent developmental disabilities of autism, enabling those children to live full and productive lives.

Thank you, Mr. Chairman and members of the committee.

Mr. BURTON. Thank you, Dr. Boyle.

Dr. Offit.

[The prepared statement of Ms. Boyle follows:]

TESTIMONY OF

COLEEN BOYLE, PhD

CHIEF, DEVELOPMENTAL DISABILITIES BRANCH

DIVISION OF BIRTH DEFECTS, CHILD DEVELOPMENT,

AND DISABILITY AND HEALTH

NATIONAL CENTER FOR ENVIRONMENTAL HEALTH

CENTERS FOR DISEASE CONTROL AND PREVENTION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

COMMITTEE ON GOVERNMENT REFORM

U.S. HOUSE OF REPRESENTATIVES

April 6, 2000

Good morning, Mr. Chairman, and Members of the Committee. I am Dr. Coleen Boyle, Chief of the Developmental Disabilities Branch of the National Center for Environmental Health (NCEH), Centers for Disease Control and Prevention (CDC). I am accompanied by Dr. Ben Schwartz, Acting Director of the Epidemiology and Surveillance Division of the National Immunization Program (NIP), CDC. Thank you for giving me an opportunity to discuss the work that we are doing at CDC in the area of preventing developmental disabilities, including autism. I have actively conducted research in this area for the past three years, directing CDC's applied research in developmental disabilities for 10 years. Developmental disabilities prevent children from achieving at the level of their peers and through no fault of their own cause a tremendous burden on families and our society in general.

Developmental disabilities are a diverse group of physical, cognitive, psychological, sensory and speech impairments that are usually identified between birth and up to age 18 years. It is estimated that about 17% of all children have a developmental disability, and 2% have a serious developmental disability such as mental retardation, cerebral palsy or autism. In most cases, we do not know the cause of the developmental disability. Several infectious diseases are known to cause developmental disabilities, including *Haemophilus influenzae* type B and congenital rubella syndrome, a known cause of autism. Other known causes of developmental disabilities include nutritional deficiencies such as those of iodine and iron, and environmental exposures including lead and mercury. Autism and conditions related to autism represent some of the most serious of these developmental disabilities. Autism is a life-long disability characterized by impairments in social interaction and communication and a pattern of restrictive, repetitive and stereotypic behaviors, interests, and activities. The impact and burden of autism on children and their families is tremendous. Most children with autism require long term care and services, including special education and supervised care.

Developmental disabilities are costly to society and to families. Local, state and federal education departments spent approximately $49.2 billion in the 1998-99 school year on special education programs for children with developmental disabilities. The cost of special education for a child with autism is often more than $30,000 per year to the family and the community, and the cost of residential care, which many of these children require, is $80,000 to $100,000 per year. There is no cure for autism; however, recent studies suggest that early intense behavioral interventions benefit some children with autism.

CDC's role in preventing developmental disabilities, including autism, is to determine the scope of the problem, identify preventable causes of developmental disabilities, and establish and evaluate intervention programs. We do this using the public health tools of population-based surveillance, epidemiologic investigations, and prevention programs.

PREVALENCE OF AUTISM

Much attention has been focused on whether there is a higher rate of autism than previously thought. Researchers conducted the first epidemiologic study of autism in England in 1966 and found the autism rate in the general population to be 4 to 5 per 10,000 children. Other early community studies published also yielded prevalence rates in this range. In general, these studies defined autism using a narrow set of criteria – which included marked impairment in social contact and elaborate behaviors or mannerisms. Studies published since 1985 outside the United States reported higher prevalence rates than those prior to 1985, about 12 per 10,000 children, while a few very recent studies have found rates that are even higher.

It is unclear why the more recent studies have yielded higher rates. However, we do know that more recent studies have used diagnostic criteria for autism which are considerably broader and incorporate the clinical recognition that the hallmark features for autism can occur in a wide range of severity levels and in many different manifestations. Clearly, a greater awareness and better recognition of this condition also have had an impact on the reported prevalence rates.

There have been only two population-based prevalence studies of autism in the U.S. Both studies were conducted in the 1980s and yielded prevalence rates of 3.3 and 1.2 per 10,000 children, which is lower than most European studies. The U.S. studies relied on identification of children with autism already known to service providers - which may account for the relatively low prevalence rate.

However, other U.S. data sources seem to support the idea that the prevalence of autism is higher than previously thought. A recent report from the California Health and Human Services Agency examined the number of people with autism entering the California Developmental Services system each year from 1987 to 1998 and showed an overall increase of 273%, with increases every year since 1987. Services for all other developmental disabilities increased no more than 50% during this time period. The State of California has contracted with the Medical Investigation of Neurodevelopmental Disorders (M.I.N.D.) Institute of the University of California at Davis to conduct a study to determine the factors accounting for the increased caseload of children with autism in California. Similarly, service provider data from the US Department of Education showed that the number of U.S. children with autism who received special education services increased 556% from 1991 through 1997.

While we cannot be certain of the reason for changes in prevalence rate, some percentage of the increase seems related to broadening of the definition of autism, changes in referral patterns, improved recognition and greater awareness of the condition. Other factors may involve eligibility and reporting requirements for disability services, changes in population demographics and patterns of migration. Genetic and environmental factors may also be contributing to an increase in the number of children with autism, which may result in larger numbers of individuals being identified. Ongoing population-based surveillance, using standard methods of case ascertainment, is needed to better understand trends in autism rates as well as other developmental disabilities.

CDC'S EFFORTS TO DETERMINE THE PREVALENCE OF AUTISM

CDC is developing reliable estimates of the prevalence of autism. In 1998 we added autism to CDC's Metropolitan Atlanta Developmental Disabilities Surveillance Program (MADDSP). This program also monitors the prevalence of mental retardation, cerebral palsy, vision impairment, and hearing impairment among school-age children. MADDSP is the only ongoing population-based study of multiple disabilities in school-age children in the United States. Information on children with developmental disabilities, including autism, is obtained by review of records from service providers in metropolitan Atlanta and identification of children with developmental disabilities in the public school system. CDC expects to publish the results of this first population-based prevalence study later this year. CDC is also funding Marshall University to begin a surveillance program for autism in six counties in West Virginia. CDC believes population-based surveillance for developmental disabilities is a critical element in preventing this disorder.

THE BRICK TOWNSHIP INVESTIGATION

Mr. Chairman, beginning in early 1998, as you are probably aware, CDC and the Agency for Toxic Substances and Disease Registry (ATSDR) were contacted by the New Jersey Department of Health and Human Services, U.S. Senator Robert Torricelli, and U.S. Representative Christopher Smith regarding the possibility of federal assistance in addressing issues raised by the citizens of Brick Township, New Jersey. They were concerned that the number of children with autism in Brick Township could be several times higher than expected based on available U.S. prevalence rates for the disorder. CDC assistance was requested because of the complexity of investigating a behavioral disorder such as autism, and because of the fact that CDC was developing epidemiologic methods that address the unique challenges of autism. ATSDR's expertise was requested because community members felt that environmental factors related to potential hazardous waste sites might be involved. CDC investigators with expertise in population-based studies of autism were responsible for the prevalence investigation. The prevalence investigation identified children with possible autism spectrum disorders whose parents were residents of Brick Township during 1998. The autism diagnosis was verified through a clinical assessment. ATSDR has conducted a scientific literature review to determine what is known about associations between chemical contaminants and autism. ATSDR has been assessing potential exposure pathways for sources of environmental pollution in Brick Township, and also is assessing whether the potential exposure pathways could be associated with the homes where children with autism lived. Specifically, three potential sources of environmental pollution were identified: (1) the municipal drinking water supply, (2) the Metedeconk River, and (3) the Brick Township Landfill. Possible exposure pathways include recreational uses of the river where contaminants may have been discharged, as well as the use of the river as a source of drinking water supply.

The report of the findings from the investigation and environmental public health assessment are currently being reviewed. The reports will be provided to the parents whose children were a part of this investigation in Brick Township and to the general public as soon as possible. We would be pleased to brief interested Members or their staff on the results at the same time we make them available to the affected community.

CAUSES OF AUTISM

The cause of autism remains unknown for most children. Several studies support an underlying genetic mechanism for autism. Studies indicate that family members of individuals with autism also are more likely than others to be diagnosed with the disorder. An identical twin of a child with autism has a 75 to 90 percent chance of having autism as well. A fraternal twin of a child with autism has a 5 to 10 percent chance of having autism. Similar genetic susceptibility may extend to other developmental disabilities as well. Among families with autism there is a 10 to 40 percent increase in the diagnosis of other developmental and learning disabilities, such as language delays and learning disabilities. Autism tends to occur more frequently than expected among individuals with certain medical conditions such as Fragile X syndrome, untreated phenylketonuria, congenital rubella syndrome, and certain seizure disorders.

A scientific literature review has identified limited evidence that certain agents ingested by pregnant women such as lead, alcohol and the prescription drug thalidomide may cause autism in their children. Such evidence, as well as prevailing theories about autism etiology, suggest that events during development in utero, especially in the earliest stages, play a substantial role in the cause of autism. Less information is known about postnatal exposure and autism. Little research has been done in the area of environmental contaminants and more is needed. In addition, it is important to do carefully controlled studies on the potential causes of autism to determine whether children exposed to a given risk factor are more likely to develop autism than children who are not exposed.

BENEFITS OF VACCINES

One of the most effective, proven ways parents can protect their children from certain infectious diseases is to ensure they receive all of their recommended vaccines on schedule. The threats posed by vaccine-preventable diseases are known and real. The viruses and bacteria that cause vaccine-preventable diseases still circulate in the U.S. and around the world. High rates of measles vaccination have protected U.S. children and communities from sustained outbreaks. In 1998 and 1999, 16 measles outbreaks and 13 rubella outbreaks in the U.S. were reported to CDC. Measles is not a benign childhood illness. It can have serious complications, including pneumonia, ear infections, brain damage, seizures and even death. A measles epidemic in the United States led to more than 55,000 cases of measles, more than 11,000 hospitalizations, and more than 120 deaths in the three years from 1989 to 1991. Measles still accounts for approximately 750,000 deaths each year globally, and congenital rubella syndrome results in severe disability or death for over 200,000 infants per year. Common manifestations of congenital rubella syndrome include deafness, blindness, heart defects, and mental retardation. Continued high U.S. vaccination rates are crucial to prevent the spread of these diseases among U.S. children. Vaccinations protect individuals and communities from diseases spread by person-to-person transmission. An individual's vaccination not only protects that individual from diseases spread by person-to-person transmission, but also adds to the protection of the rest of the community. A decision to not vaccinate places individuals and communities at risk.

CDC'S MISSION TO ENSURE SAFE VACCINES

The public should expect that we will do all we can to deliver safe vaccines. While vaccines are among the safest pharmacologic interventions for disease prevention available, no drug or vaccine is 100 percent without risk. Extensive pre-market studies of vaccine safety are conducted and carefully reviewed by FDA before a vaccine is licensed. Post-marketing evaluation of vaccine safety is also conducted. CDC and FDA have developed an infrastructure to continue monitoring vaccine safety. This includes the Vaccine Adverse Event Reporting System (VAERS), a nationwide, passive surveillance system that provides "signals" of potential vaccine adverse events; and the Vaccine Safety Datalink, an active surveillance system that links vaccination and health data from four large Health Maintenance Organizations and which can be analyzed to assess whether an association exists between vaccination and an adverse event. In addition, targeted epidemiological studies using case-control or cohort methodologies are also conducted to investigate specific concerns.

These methods have been used to further enhance the safety of the vaccination program. Examples of changes that have been made to improve the safety of the vaccination program include a shift from whole cell pertussis vaccines to a less reactogenic acellular vaccine; a change from oral to injected poliovirus vaccine to prevent vaccine-associated paralytic polio; and the withdrawal of recommendations for rotavirus vaccine after investigations showed that vaccination increased the risk of intussusception, a form of bowel obstruction among infants. These examples demonstrate the commitment of CDC and partner agencies to assuring vaccine safety and the flexibility of the program to respond to safety issues that have been scientifically documented.

SCIENTIFIC EVIDENCE REGARDING VACCINES AND AUTISM

Currently available scientific evidence does not support a link between vaccination and autism or any other behavior disorder. This statement is based on the following synopsis of published data:

- An initial observation linking autism and MMR vaccine was reported by Dr. Andrew

Wakefield and colleagues, who had first attempted to link measles disease and vaccination to inflammatory bowel diseases such as Crohn's Disease. Dr. Wakefield suggested that measles/mumps/rubella (MMR) vaccination led to intestinal abnormalities, resulting in impaired intestinal function and developmental regression within 24 hours to a few weeks of vaccination. This hypothesis, which suggested that children developed autism shortly after receipt of MMR vaccine, was based on a case-series (a collection of patients with limited comparison or control groups) reporting data from 12 children.

The Working Party on MMR vaccine of the British Committee on Safety of Medicines conducted a systematic review of reports of autism, gastrointestinal disease and similar disorders after receipt of MMR or measles/rubella (MR) vaccine. In 1999, the Working Party concluded that the information available "...did not support the suggested causal association or give cause for concern about the safety of MMR or MR vaccines."

A study published in 1999 in *The Lancet* by Dr. Brent Taylor and colleagues provides population-based evidence that overcomes a number of limitations that the Working Party and the Wakefield group experienced. The authors identified all 498 known cases of autism spectrum disorders (ASD) in children living in certain districts of London who were born in 1979 or later and correlated the cases to an independent vaccination registry. The results of this study were:

1. The first diagnosis of autism or initial signs of behavioral regression were not more likely to occur within time periods following MMR vaccination than during other time periods.

2. Despite an increase in the number of diagnosed ASD cases since 1979, no jump occurred after the introduction of the MMR vaccine in 1988. Such a jump would have been expected if MMR was causing a substantial increase in autism causes, but this was not the case.

3. Children who were vaccinated before 18 months of age were diagnosed with autism at ages similar to children who were vaccinated after 18 months of age, indicating that the vaccination did not result in earlier expression of ASD characteristics. If MMR were causing many autism cases, it would have been expected that children vaccinated at a younger age would develop autism at a younger age than children vaccinated at older ages, but this was not the case.

4. At age two, the MMR vaccination coverage rates among ASD cases were nearly identical to vaccination coverage rates of children in the same age group in the whole region, providing evidence of a lack of overall association between ASD and the MMR vaccination. If MMR was a major cause of autism, then it would have been expected that cases of autism would be more likely to be vaccinated than the general population, but this was not the case.

- Another study, conducted by Dr. Christopher Gillberg and Dr. Harald Heijbel, also showed no evidence of association between the MMR vaccine and autism. The study compared autism prevalence rates in populations of children from two communities in Sweden. The results indicated no difference in autism prevalence between children born after the introduction of the MMR vaccine in Sweden and those born before the vaccine was used. The study was published in the journal *Autism* in 1998.

At this time, the weight of scientific evidence does not support an association between MMR and autism.

WHAT RESEARCH IS CDC CONDUCTING ON VACCINATION AND AUTISM?

Many parents remain concerned that their child's autistic behaviors seemed to occur or to worsen shortly after vaccination. Despite the fact that the available evidence, on balance, does not support a causal link between vaccines and autism, given the level of concern, it is critical to investigate this issue more fully using the best scientific methods available. The challenge of vaccine safety research is to use scientifically sound methodologies to investigate uncommon events and to distinguish events that would have occurred anyway even without vaccination from those that are truly causally related.

One important ongoing CDC study is based on CDC's population-based autism surveillance system in metropolitan Atlanta – one of few such surveillance systems in the world. The system began to identify cases of autism in 1998 among children between 3 and 10 years old in the metropolitan Atlanta area. Children with autism are identified through special education records of all area public schools and other sources. Capitalizing on this unique resource, CDC has initiated an epidemiologic study with the primary objective of evaluating the association between MMR vaccination and autism. The study will compare the vaccination histories of over 500 children with autism and over 1500 control children matched on school, age, gender, and the children's schools. Data collection is nearing completion and the study results are expected later this year.

In addition, CDC is working with the National Institutes of Health to develop a study that will evaluate whether vaccination is linked with developmental regression. These studies, and a CDC study of inflammatory bowel disease and MMR vaccination using the Vaccine Safety Datalink, demonstrate CDC's ongoing commitment to assuring the safety of the vaccination program.

Given the balance of available scientific data and the known serious and ongoing risk of vaccine preventable diseases, the best public health policy is to continue vaccination schedules unchanged while we continue to monitor vaccine safety. This approach, we believe, is most effective in protecting the overall health of children and reflects the strategy of other countries such as the United Kingdom, which also has considered these questions.

CONCLUSION

Mr. Chairman, in the past 40 years, public health has made significant advances in preventing developmental disabilities. Identification and prevention of congenital syphilis and congenital rubella syndrome have spared the lives and prevented disabilities for thousands of children. Newborn screening programs have prevented life-long mental retardation and prolonged the lives of tens of thousands of children with metabolic disorders, such as hypothyroidism, PKU, and sickle cell disease. However, even though this is good news, we still don't know the causes of most developmental disabilities, including autism. CDC agrees with the Committee that autism is a serious developmental disability that has a significant and profound impact on the lives of not only the child with the disorder, but also the child's family. We must develop a better understanding of autism and its causes. We need to track this disorder, identify preventable causes, and institute effective intervention programs. CDC is using available resources to develop surveillance systems to collect information so that we can better understand what is happening with the prevalence rate over time. We must also conduct epidemiological studies to begin to uncover the causes of this serious developmental disability. It is my hope that this work, combined with scientific investigations conducted by other federal agencies such as NIH and within the academic community, will lead to identifying what causes autism, preventing this disorder, and enabling these children to live full and productive lives.

Thank you, Mr. Chairman and members of the Committee, for the opportunity to testify before you today about CDC's efforts to better understand and prevent this serious developmental disability. I am happy to answer any questions you might have.

Dr. OFFIT. First, I would like to recognize the courage of the parents who have testified her today, as well as the two grandparents on the committee, including you, Mr. Chairman. As I share my testimony, I also deeply share their feelings and concerns.

My name is Paul Offit. I am pediatrician, and I am also the chief of infectious diseases and the Henle professor of immunologic and infectious diseases at the Children's Hospital of Philadelphia and the University of Pennsylvania School of Medicine. In addition, I am a member of the Advisory Committee on Immunization Practices to the CDC. I have 20 years of experience in the areas of virology and immunology.

My role in these proceedings is to explore the theories that have arisen due to concerns by the public that autism might be caused by the combination of measles, mumps, and rubella vaccines known as MMR.

No evidence exists which proves this association. However, three theories have been used to explain it. In the time that I have been given, I would like to explain why I think that these theories are not valid.

The first theory is that children who get the measles vaccine make an immune response not only to the vaccine, but also to their own nervous system. This kind of reaction is called autoimmunity. To understand why this theory is invalid, we must first understand differences between natural measles infection and measles vaccination.

During natural measles infection, the measles virus reproduces itself many times in the body and causes disease. In contrast, following measles vaccination, the vaccine virus reproduces itself much less and does not cause disease. Because more measles proteins are made during natural infection than after immunization, the immune response to natural infection is greater than the immune response to immunization. If the immune response is greater after natural infection, then the autoimmune response would also be greater. If this were the case, then autoimmunity should occur more frequently after natural infection than after vaccination. Or, said another way, if measles virus caused autism, then measles vaccination would lower, not raise, the incidence of autism.

The second theory is that the child's immune system is simply overwhelmed by seeing three viruses in a vaccine at the same time. Some have gone so far as to suggest that it may be of benefit to divide the MMR vaccine into three separate vaccines. The rationale behind this theory is that children do not normally encounter such an assault on their immune system.

From the birth canal and beyond, infants are confronted by a host of different challenges to their immune system. Their intestines encounter foreign proteins in milk and formula. Their lungs encounter bacteria inhaled on the surface of dust in the air. And literally thousands of different bacteria immediately start to live on the skin as well as on the lining of the nose, throat, and intestines.

Here is how infants deal with this immediate confrontation to their immune system. Babies have a tremendous capacity to respond to their environment from the minute they are born. The newborn has billions of immunologic cells which are capable of responding to millions of different microorganisms. By quickly making an immune response to bacteria that live on the surface of their intestines, babies keep these bacteria from invading their bloodstream and causing serious disease.

Therefore, the combination of the three vaccines contained in MMR, or even the 10 vaccines given in the first 2 years of life, is literally a raindrop in the ocean of what infants successfully encounter in their environment every day.

The third theory is that the MMR vaccine is given by an unnatural route. The rationale behind this theory is that children do not normally encounter viruses or bacteria under their skin or in their muscles. But infants and children frequently encounter viruses and bacteria in many places throughout the body. Our species survives because from the minute we are born, we are capable of meeting challenges at all sites.

To review, here are the medical facts. First, if autism is a consequence of autoimmunity, the incidence of autism would have decreased, not increased, after vaccination.

Second, children from birth are confronted with and manage an enormous array of different challenges to their immune system at the same time.

Third, challenges to their immune system occur by a variety of routes.

The parents we have heard testify here today are asking a scientific question: Does the MMR vaccine cause autism? Questions of science are best answered by scientific studies, and the answer to this question is already available. Dr. Brent Taylor and his coworkers in London have conducted a large, meticulously designed, well-controlled study that disproves an association between MMR vaccine and autism. I believe other studies will confirm Dr. Taylor's results, because it is important to have confirmatory studies.

What is really at stake here? In the early 1990's, our immunization rates against measles dropped only about 10 percent. Measles outbreaks swept across the country. About 11,000 people were hospitalized, and 123 died from measles—died from a disease which is easily and safely prevented by a vaccine.

My concern, Mr. Chairman, is that parents listening to or reading about this hearing might incorrectly conclude that vaccines cause autism. This is not the case. Vaccines are extremely safe and highly effective. I encourage this committee to make that fact clear to every parent in America.

If, as a result of reading about this hearing, some parents choose to withhold or delay vaccines for their children, their tragedy could be profound. If many parents choose to withhold vaccines, the tragedy all across America could be devastating.

Let us proceed cautiously, carefully, and scientifically.

Thank you.

Mr. BURTON. Thank you.

Dr. Taylor.

[The prepared statement of Dr. Offit follows:]

Dr. Paul A. Offit
Testimony to
Government Reform Committee
Autism – Present Challenges, Future Needs – Why the Increased Rates?
April 6, 2000

My name is Paul Offit. I am a practicing pediatrician. I am also the Chief of Infectious Diseases and the Henle Professor of Immunologic and Infectious Diseases at The Children's Hospital of Philadelphia and the University of Pennsylvania School of Medicine, and a member of the Advisory Committee on Immunization Practices to the CDC. I am also the co-author of a book entitled "*Vaccines: What Every Parent Should Know*". My expertise is in the areas of virology and immunology.

In addition, I have been in collaboration with Merck and Co. on the development of a rotavirus vaccine since 1992. My interest in this project is to prevent rotavirus disease. In developing countries rotavirus infections kill about 14 children every day. In fact, more children die every day from rotavirus infections than from any other single infectious disease. In the United States, about 1 out of every 75 children born will be hospitalized with severe water loss (or dehydration) as a result of rotavirus infections. We hope that by developing this vaccine we can prevent the severe disease and death caused by this virus.

My role in these proceedings is to explore the theories that have arisen due to concerns by the public that autism might be caused by the combination of measles, mumps, and rubella vaccines (known as MMR). No evidence exists that proves this association. However, three theories have been used to explain it. In the time that I have been given, I would like to explain why I think that these theories are not valid.

The first theory is that children who get the measles vaccine make an immune response not only to the vaccine, but also to their own nervous system. This kind of reaction is called autoimmunity. To understand why this theory is incorrect, we must first understand differences between natural measles infection and measles vaccination.

During natural measles infection, the measles virus reproduces itself many times in the body and causes disease. In contrast, following measles vaccination, the vaccine virus reproduces itself much less and doesn't cause disease. Because more measles proteins are made during natural infection than after immunization, the immune response to natural infection is greater than the immune response to immunization.

If the immune response is greater after natural infection, then the autoimmune response would also be greater. If this were the case, then autoimmunity should occur *more* frequently after natural infection than after vaccination. Or, said another way, if measles virus caused autism, measles vaccination would *lower*, not raise, the incidence of autism.

The second theory is that the child's immune system is simply overwhelmed by seeing three viruses in a vaccine at the same time. Some have gone so far as to suggest that it may be of benefit to divide the MMR vaccine into three separate vaccines. The rationale behind this theory is that children do not normally encounter such an assault on the immune system. However, this notion is incorrect.

From the birth canal and beyond, infants are confronted by a host of different challenges to their immune system. Their intestines encounter foreign proteins in milk and formula. Their lungs encounter bacteria inhaled on the surface of dust in the air. And literally thousands of different bacteria immediately start to live on the skin, as well as on the lining of the nose, throat, and intestines. So how does the infant deal with this immediate confrontation to their immune system?

Babies have a tremendous capacity to respond to their environment from the minute they are born. The newborn has billions of immunologic cells that are capable of responding to millions of different microorganisms. By quickly making an immune response to bacteria that live on the surface of their intestines, babies keep those bacteria from invading their bloodstream and causing serious disease. Therefore, the combination of the three vaccines contained in MMR, or even the 10 vaccines given in the first 2 years of life, is literally a raindrop in the ocean of what infants successfully encounter in their environment every day.

Because the peak of some diseases (such as pertussis and *Haemophilus influenza* type b) occurs in early infancy, it is important to make sure that children are fully immunized against these diseases by 6 months of age. This is easily accomplished. About 95% of infants will develop protective antibodies following immunization because their immune systems are quite capable of responding to vaccines.

The third theory is that the MMR vaccine is given by an unnatural route. The rationale behind this theory is that children normally inhale measles, mumps, or rubella viruses carried on droplets from another person, and do not normally have virus injected under the skin. However, encountering viruses or bacteria under the skin or within the muscles does occur naturally. To meet this challenge, children have collections of immune cells in lymph glands located strategically throughout the body. For example, lymph glands are located behind the elbow and under the arm. Because our skin can be cut, our bodies are ready to encounter challenges at any site. Indeed, although wondrous, the birth process is quite traumatic. Newborns commonly have small cuts on the face and body after passing through the birth canal. Because the birth canal is covered with bacteria, the child will encounter bacteria under the skin immediately. Our species survives because, from the minute we are born, we are quite capable of meeting challenges at all sites.

To review, I have made three points that counter the plausibility that autism would be a consequence of the MMR vaccine, or, more importantly, any vaccines:

- First, if autism is a consequence of autoimmunity, then the incidence of autism would have *decreased*, not increased, after vaccination.
- Second, children from birth are confronted with an enormous array of different challenges to their immune system at the same time.
- Third, challenges to their immune system occur by a variety of routes.

These are medical facts.

Parents testifying here today are asking a scientific question, "Does the MMR vaccine cause autism?" Questions of science are best answered by scientific studies. And the answer to this question is already available. Brent Taylor and his coworkers in London have conducted a large, meticulously designed, well-controlled study that disproved an association between MMR vaccine and autism. I believe other studies will confirm Dr. Taylor's results.

We also have to ask ourselves this question, "What is really at stake here?" In the early 1990s our immunization rates against measles dropped only about 10%. When that happened, measles outbreaks swept across the country. About 11,000 people were hospitalized and 123 died from measles – *died* from a disease that is easily and safely prevented by a vaccine.

My concern, and it should be the concern of this committee, Mr. Chairman, is that some parents listening to or reading about this hearing might incorrectly conclude that vaccines cause autism. This is clearly not the case – vaccines are extremely safe and highly effective at preventing serious disease and death. I encourage this committee to make that fact clear to every parent in America.

If, as a result of reading about this hearing, *some* parents choose to withhold or delay vaccines for their children, their tragedy could be profound. If many parents choose to withhold vaccines, the tragedy all across America could be devastating.

Let's proceed cautiously, carefully, and scientifically.

Mr. Chairman, I am ready to respond to any questions the committee might have.

Dr. TAYLOR. Hello. I am Brent Taylor. I am the professor of community and child health at the Royal Free and University College School of Medicine and the head of the Department of Pediatrics and Child Health on the Royal Free campus of University College London.

I am honored to have the opportunity to testify today. I am here as a clinical scientist, but I am also a practicing pediatrician. My clinical work involves children with disabilities including autism.

I know how desperate families can be to understand the cause of their child's often devastating condition. I also know that if we are to avoid families being led astray by false hopes, advances in understanding and treatment must be based on high-quality and rigorous science.

Mr. Wakefield and Professor O'Leary's testimony notwithstanding, the belief that MMR is the cause of autism is a false hope.

I have four main points. We do not fully understand the reasons why autism has recently increased. We do know that there is no evidence that immunizations are involved.

Second, there is no evidence that MMR vaccine causes autism. Third, there is no conspiracy to suppress information about the side effects of vaccines—completely the reverse. Fourth, because of poor science, uptake of MMR vaccine has fallen to dangerously low levels in the United Kingdom, putting children's lives at risk from a resurgence of the damaging and occasionally killing of preventable diseases, measles, mumps, and rubella. The same thing could happen in the United States of America.

If I could have the first overhead, please.

Here are some figures from the United Kingdom. You can see at the top, in the black closed circles, MMR uptake, which has fallen from about 90 percent in 1995 to 75 percent in April 1999. There is almost an exact parallel fall—shown in the open circles—in mothers' confidence in the safety of MMR vaccine.

Could we have the next overhead on top of this one, please?

The reason for this loss of confidence relates mainly to two papers produced by Mr. Wakefield and colleagues. The first, which incorrectly related measles vaccine to Crohn's disease, one form of inflammatory bowel disease, has subsequently been completely undermined. There is no evidence that measles or measles vaccine play any part in inflammatory bowel disease.

The second arrow shows the timing of a paper produced by Mr. Wakefield and colleagues describing a small group of inadequately described children with a range of autism-related disorders.

Following each of these papers, there was a major effect on mothers' confidence and a resultant further decline in MMR uptake.

I will now discuss the results of an epidemiological study I led to test Mr. Wakefield's hypothesis that MMR causes autism. My two senior colleagues, Dr. Elizabeth Miller and Dr. Patty Farrington, have submitted testimony to this committee with details of our methods and the background of our study.

We identified all known cases of autism—498 in total—living a defined area of North London and compared details of the onset and recognition of their condition with independently collected data on exactly when they received MMR and other measles-containing vaccines. The study involved a large amount of work, and we analyzed the data in considerable depth. There are lots of results which have been published in the Lancet.

In summary, all of our analyses were negative. We concluded that MMR vaccine is not causally related to autism. In particular, we looked at the clustering after MMR of regression where it occurred, the timing of parents' concern about the child's development, and the age at diagnosis. There were no significant relationships.

Our results are supported by other studies from Sweden, from Finland, and from France.

Our particular interest in this hearing is the rise with time we identified from the late 1970's to 1992.

Could we have the next overhead, please?

Mr. Wakefield has compared our results with those reported in California. This is the overhead. It is important to remember that the authors of the California report clearly stated that theirs was not incidence data.

The overhead, which is downloaded from the Lancet Web page, is of rather poor quality, and so is Mr. Wakefield's content. He has fiddled with the data regarding the dates of the introduction of autism, and to demonstrate other problems he has with time relationships, it is worthwhile just looking at the bottom line, where it goes from 1987 to 1960 to 1990. What is actually going on?

I have included two additional arrows, the red arrows, which perhaps more accurately identifies the acceleration in cases in the rates at which autism is increasing. These, one can see, occurred at least 2 years before autism was introduced into the United Kingdom and at least 2 years after in California—hardly a convincing causal relationship.

There is another problem for the MMR theory. Could we have the next overhead, please?

Here is our data from our study up until 1992, which is what we published. The rise in autism can be seen there as clearly occurring long before MMR was introduced, and I must say, contrary to what Mr. Wakefield and some of the groups he is associated with say, that we included all cases in our analysis, including those involved in the MMR Catch-Up Campaign.

After 1992, the numbers fell. We did not include these data in our analysis because we felt that there might be too many missing cases not yet diagnosed, and by leaving the left-hand side, it really gave the hypothesis that MMR causes autism the best chance of being confirmed.

The parallel line in red is data from two of the larger districts, and this is important, because we have preliminary data as part of the further study on the same population to see what has happened. Is autism still going up, or is it flattening out?

What our early results in these two districts show—if we could have the final overhead—is that rates are going down. There is an overall increase of numbers, reflecting continuing better recognition of autism, and immigration. The fall is seen in both studies, suggesting it is a real fall. Cases appear in this population to have peaked in about 1992, for reasons which are quite unclear.

This finding alone must exclude MMR as a cause of autism. MMR had a rapid uptake in our population from 1988; then, rates plateaued, certainly until 1995, while autism rates were rising and then falling.

We need more research on autism and its treatment, but Mr. Chairman and members of the committee, present evidence does not support a causal relationship between MMR vaccine and autism. As a result of adverse publicity on this topic, many clients in the UK are now at risk from the dangerous diseases of measles, mumps, and rubella. I urge this committee to strongly support the continued MMR program to avoid putting America children's lives at risk.

As a result of my work and clear study of the evidence on this topic, I believe I can say with confidence that MMR vaccine is not a cause of autism.

[The prepared statement of Dr. Taylor follows:]

Testimony to the Congress of the United States House of Representatives Committee on Government Reform

Hearing on: "The challenges of autism. Why the increased rates?"

Brent Taylor
Professor of Community Child Health
Royal Free and University College Medical School
University College London, London NW3 2PF, United Kingdom

6 April 2000

Introduction

I am honoured to have the opportunity to speak today. I am here to testify mainly as a clinical scientist but I am also a practising paediatrician and have been for over thirty years. My clinical work mainly involves children with disabilities including autism and related conditions. I know the devastating impact autism can have on children and families and how desperate families can be to identify the reason why their child developed the condition.

The main thrust of my research activity over many years has been the identification of risk factors in early life which might influence subsequent health and development in childhood into adult life and which can be altered, with implications for prevention. This is a complex area of research. It is all too easy to draw simplistic conclusions from time relationships such as the introduction of MMR vaccine and the apparent rise in the prevalence of autism. Such a relationship is most likely not to be causal but only an association. Statistical analysis, particularly in this area, needs careful interpretation.

Four main points:

I would like to make four main points in relation to the apparent rise in autism, particularly in relation to the possible role of vaccines and immunizations:

1. Recorded rates of autism have recently increased. This may reflect increased knowledge about the wide range of abilities of people with autism, with more professionals trained and willing to recognise the condition, or may, at least in part, be real. Preliminary data from North London suggests that rates there may now be falling. There is no valid scientific evidence that the change in rates relates to vaccines or to immunization.

2. There is no satisfactory evidence that MMR vaccine causes autism (or bowel disease). Parents whose children have autism can be reassured that they did not cause their child's condition by allowing him or her to be immunized.
3. There is no conspiracy to suppress information about the side-effects of vaccines, indeed the scientific community is looking very carefully and critically for adverse effects.
4. Uptake of vaccines has fallen dangerously in the UK because of the publicity associated with poor science suggesting that there is a relationship between MMR vaccine and autism and/or inflammatory bowel disease. Supportive statements from influential bodies like this committee could prevent the same thing happening in the USA

Background:

Vaccination and vaccine safety are issues of major concern to the public, their elected representatives and all health care workers. I have recently undertaken, with colleagues from the UK's Public Health Laboratory Service and the Open University, a study of the possible relationship between MMR vaccine and the onset of autism in North East London. This work has been funded by the UK's Medicines Control Agency, a body charged with assessing the safety of products used for medical treatments, and linked to the Department of Health.

The stimulus to this work was the hypothesis by Wakefield and colleagues that MMR vaccination might be causally linked with autism. They had found such a relationship in eight of twelve children with autistic conditions investigated because of associated bowel symptoms. Their group of children has never been adequately described and seems very unlikely to be a representative sample of children with autism. The authors stated in their paper that they had not proved a causal association but the resultant media attention resulting from this work, and earlier work from the same investigators suggesting an association between measles-containing vaccines and inflammatory bowel disease (work not confirmed in their subsequent studies, or by anyone else, anywhere), has had a dramatic effect on public confidence in MMR vaccine and on immunisation uptake as demonstrated in figure 1.

Epidemiological study investigating the relationship between MMR vaccination and the onset of autism: I will now describe our study which has been published in The Lancet (12 June 1999). We identified all known children with autistic spectrum disorder, a total of 498 individuals up to 19 years old, in the population of North East London. We examined their medical records recording the age at which the parents became concerned about the child's development, the age at which the diagnosis of autism was made and, in the third of cases where it was a feature, the age at which the child's development regressed. We compared this information which was recorded before the recent concern about immunization, with independently collected data on exactly when the child received MMR vaccine or other measles-containing vaccines. Thus this was a properly conducted population-based epidemiological study.

We undertook four main analyses. The most direct assessment, and therefore our most important result, was that there was no clustering of development regression in the months after vaccination, no increased likelihood of autism diagnosis within one or two years after vaccination and, with a single statistical blip to be explained later in this paper, no increased likelihood of parental concern within six or twelve months of vaccination.

Other negative results included no difference between the age at diagnosis in vaccinated and unvaccinated children with autism, closely similar MMR uptake in the children with autism and in the general population (Figure 2), and no change in time-trend, that is no step up in the numbers of cases identified with autism, when the MMR vaccine was introduced to the UK in October 1988; this lack of effect from MMR is shown in Figure 3

Our study has been criticised by a few individuals and groups who still believe that MMR causes autism. It has been suggested that we failed to consider older children who were immunised as part of the catch-up programme when the MMR vaccine was introduced. This is not so. We identified all 36 such children with autism in our study who received MMR. Age at parental concern about the child's development was recorded in 29 of these. In all 29 cases the parents were concerned before the child was vaccinated.

Apparent rise in the prevalence of autism:

Of major interest to this hearing is the identification in our study of an apparent marked increase in the numbers of children with autism by year of birth. We believe this partly, at least, reflects increased recognition and better recording of individuals with the condition. We used current disability registers, many now computerised, to identify the children. These registers have undergone considerable development over recent years but tend to concentrate on younger children. Thus older children with autism, many of whom are educated away from their normal place of residence and who may not be known to local services, might not be recognised by such a study. Thus identification of cases in our published study is unlikely to be complete but this will not have affected our results regarding MMR vaccination.

The increase we described matches the recent increase in the number of cases with autistic spectrum disorder identified in California. Wakefield has compared our results with the California study and has suggested that the rise in both parts of the world coincided with the introduction of MMR. Figure 4 shows his graph. I have inserted two other arrows which more accurately identify the time of the apparent increase in autism; three years after the introduction of MMR in California and two years before the introduction of MMR in the United Kingdom – hardly a convincing causal relationship. In general little can be learned about possible causality by comparing such time-relationships which are likely to be only coincidences – with many alternative possible explanations as well as the one the enthusiast is promoting. More direct investigation is required such as the study we conducted.

Statistical artifacts:

Wakefield and groups he is associated with have made much of a marginal positive statistical association in our paper relating parental concern with MMR vaccination within six months. This was one of 14 such analyses and with so many analyses one might have expected a positive statistical association by chance. We have considered this single positive result in great detail and consider it to be a statistical artifact reflecting the tendency for parents when recalling symptoms many months after the event to round up to twelve months, eighteen months, twenty-four months and the like. This is shown in figure 5 which also shows that the average age for MMR vaccination was 13 months.

A positive association was only seen for the particular interval, 13 months and 18 months. It did not occur, for example, if the child received MMR vaccine at 14 months with parental concern at 19 months. No biological process can be so time-specific. It was not seen with other measles-containing vaccines because these earlier vaccinations were given over a wider time range than MMR so the co-incidental time-relationship of vaccination at 13 months and parental concern at 18 months could not occur. MMR vaccine is given in the second year of life which is the age when symptoms of autism often become manifest. The relationship is a statistical association – a co-incidence, not a causal relationship.

Californian report not an incidence study:

The report by the Department of Developmental Services in California clearly stated that theirs was not an incidence study. "*The quality and type of information examined in this report were not suitable for measuring incidences in the population of persons with autism. Ascertaining the incidence of autism and the other PDDs will require carefully controlled research ... Speculation about the rise in numbers is abundant, but such speculation is not based on scientific research*". Our UK study is consistent with an increase in the incidence of autism in recent birth cohorts up until 1992. That increase may be real or mainly a reflection of other factors such as better recording and case identification arrangements in recent years. However, whether real or artifactual, the trend in increasing incidence with successive birth cohorts to 1992 was not related to the introduction of MMR vaccine or to vaccine coverage, which reached a plateau during the period in which autism incidence was apparently increasing.

Recent preliminary evidence that rates of autism are now falling:

Our Lancet paper used data up until 1992 although we collected data up until the end of 1997. We selected 1992 as a cut-off to provide the best possible chance to confirm the hypothesis that MMR was the cause of autism. We could not do so. Additional, unpublished data from our study, shown in figure 6, showed a subsequent marked decline in the number of identified cases with autism. We thought this might reflect delays in diagnosis inherent to the disorders. However we are in the process of repeating our prevalence study in the same population and preliminary results in a sample of districts suggest that the peak about 1992 has been followed by a real decline in cases by year of birth as shown in figure 7. These findings exclude a causal influence from MMR or any other vaccine as coverage has been stable while rates of autism have climbed and are now going down. It is hard to see how one could cause the other.

Independent support for and validation of our results:

Our published results confirm and extend studies from Sweden (Gilberg and Heijbel. Autism 1998; 2: 423-424) and Finland (Peltola and others. Lancet 1998; 351: 1327-8), both of which demonstrated no relationship between MMR vaccination and autism. Other reports have found no link between measles infections, or their rare complications, and autism; nor has inflammatory bowel disease been associated with autism in epidemiological studies (Fombonne E. Journal of Autism and Developmental Disorders 1999; 29: 349-350). There was no evidence that MMR vaccination led to inflammatory bowel disease in the continuing, large, Finnish study by Peltola and colleagues mentioned above, which was established to assess the long-term efficacy and safety of MMR.

Conclusions:

Possible adverse reactions to vaccines have a particular attraction to various pressure groups and to the media with important and possibly catastrophic effects on public confidence in immunization and on vaccine uptake. Present evidence does not support a causal relationship between MMR vaccine and autism. As a result of adverse publicity on this topic many children are now at risk of these damaging and occasionally fatal diseases. I urge this Committee to support strongly the continued MMR vaccination program. I certainly support the need for further work on identifying the cause or causes of autism, which remains elusive, and on better treatments for this often disabling group of disorders. However as a result of my work I believe I can say with confidence, that whatever causes autism, it is not MMR.

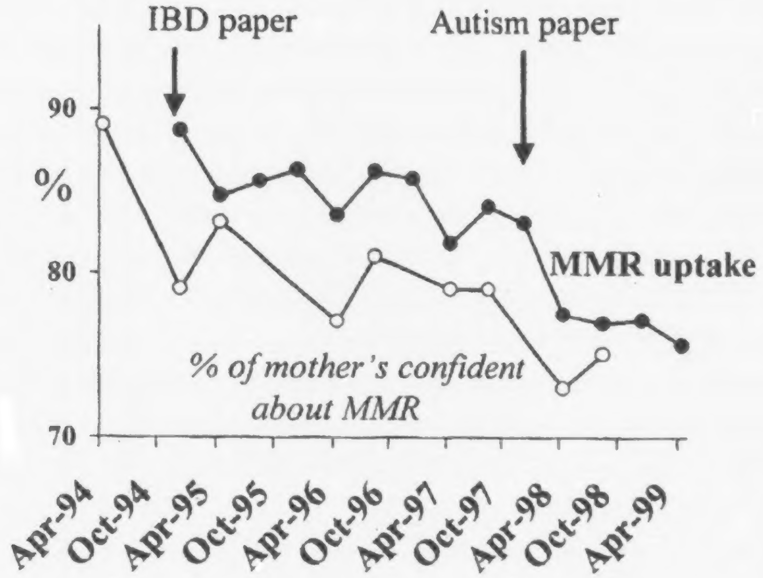


Figure 1: MMR uptake at 16 months and proportion of mothers believing in complete or almost complete safety of MMR vaccine. The figure shows the close relationship between the decline in vaccine uptake and loss of public confidence in MMR, with a major adverse effect from the media attention associated with the publication of papers suggesting that MMR vaccine caused inflammatory bowel disease and autism

Data from UK Public Health Laboratory Service COVER statistics and Health Education Authority surveys

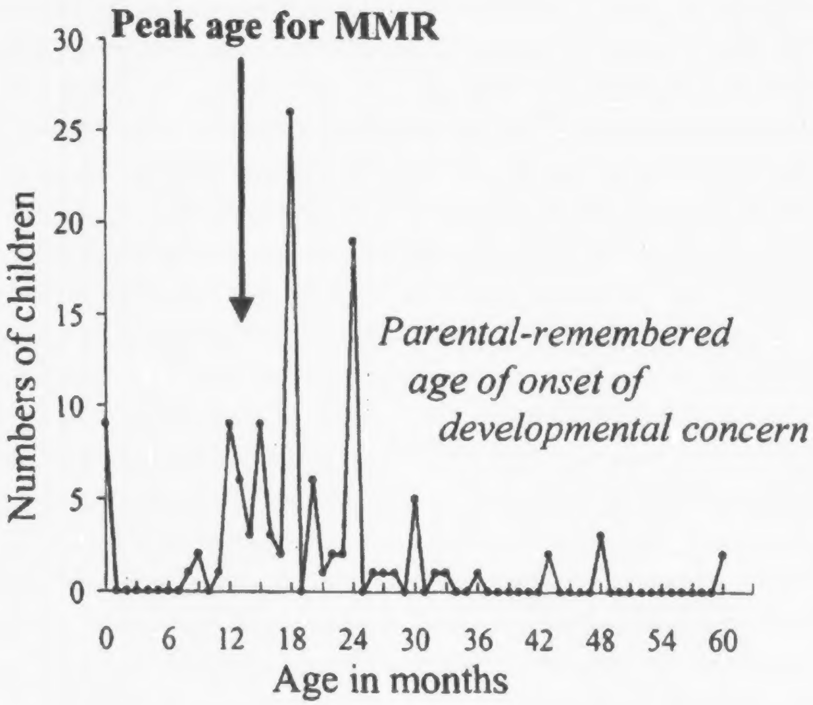


Figure 5: Autism in North East London showing the age when parents recalled concern about their child's development. Clustering is obvious at 12, 15, 24 and especially 18 months. The figure also shows the peak age of MMR vaccination at 13 months.

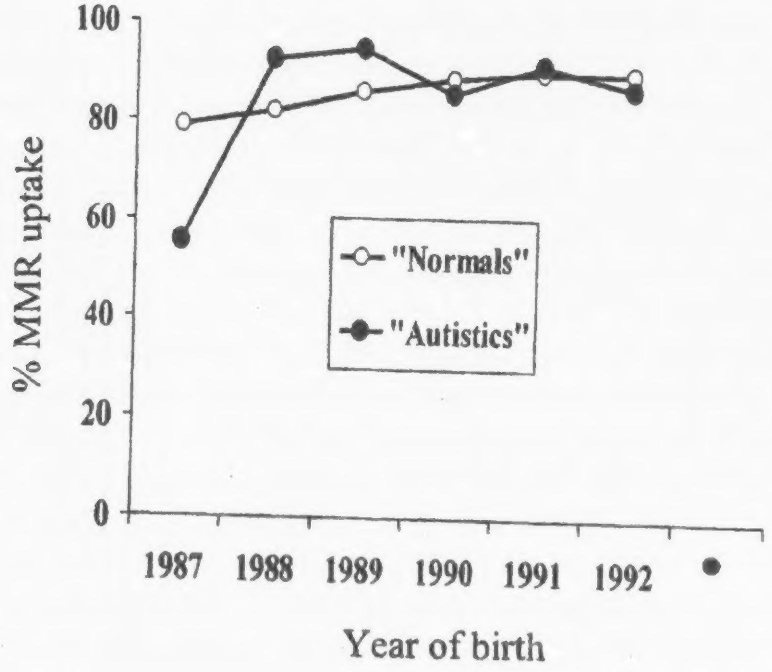


Figure 2: Closely similar MMR uptake was seen in children with autism and in the general population of North East London.

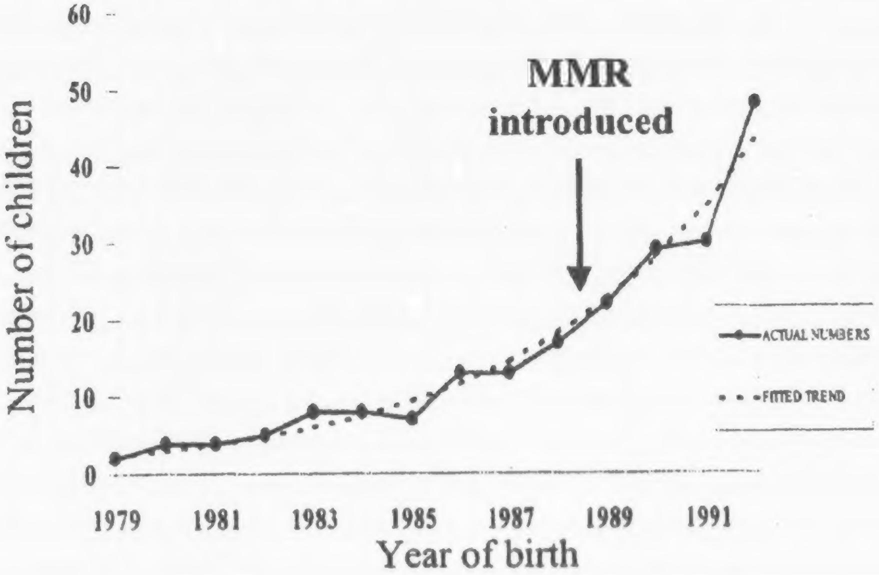
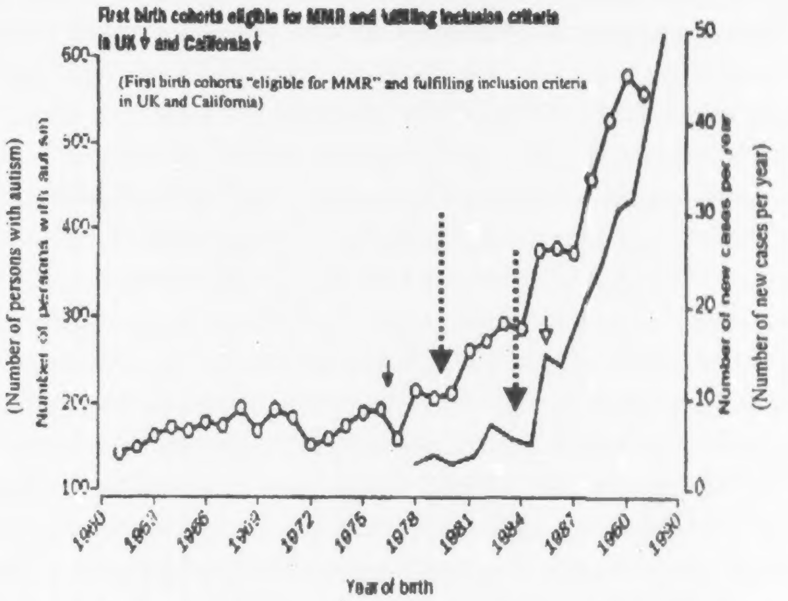


Figure 3: Cases of autism in North East London by year of birth 1979-1992, showing that the number of recorded cases was increasing before MMR vaccine was introduced and that there was no step-up when it was.



Temporal trends for autism in the USA (California*) and the UK (north-west Thames)

Figure 4: Illustration from Wakefield, Lancet, 16 September 1999, which shows an apparent rise in the prevalence of autism in California and England. Additional dotted arrows have been included to show a more likely time when autism diagnosis accelerated than Wakefield's modified link to the introduction of MMR in each country.

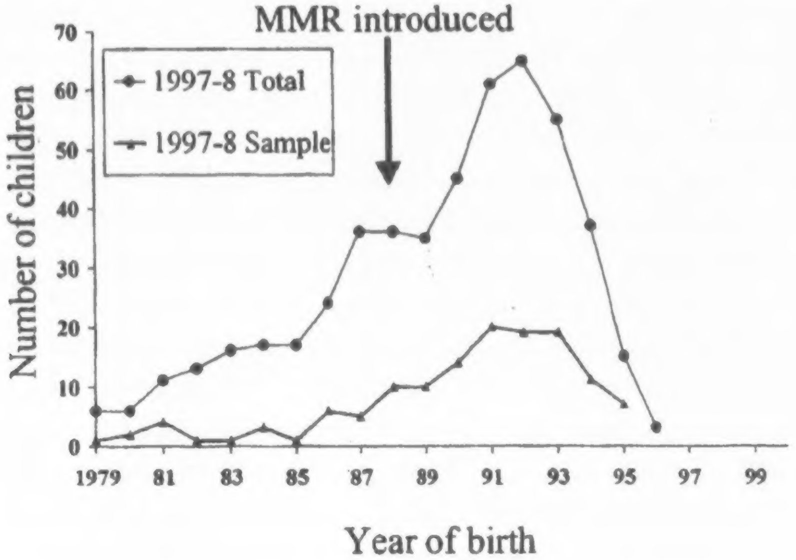


Figure 6: Autism by year of birth in North East London. Numbers were rising long before the MMR vaccine was introduced. There was a peak in numbers about 1992 with an apparent marked fall since. This is shown in the total population and in two districts where cases recently have been reviewed.

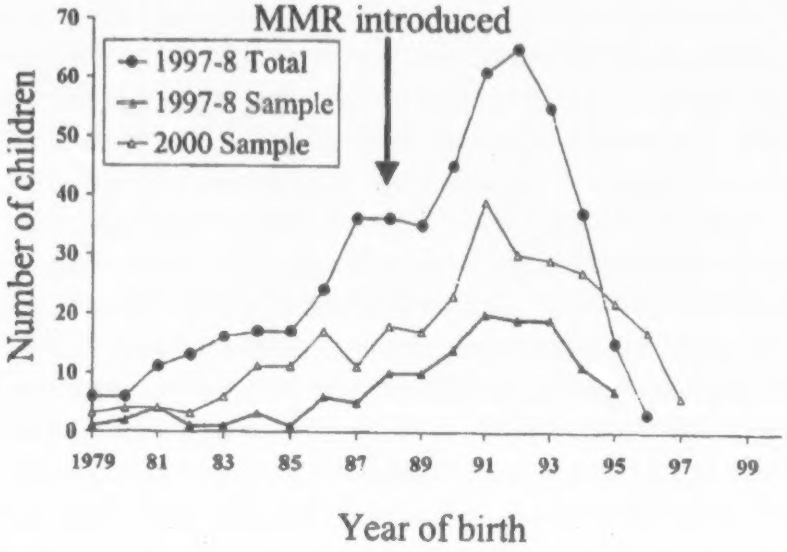


Figure 7: Autism by year of birth in North East London showing the preliminary results of the recent survey in the Sample districts. Additional cases have been identified (many having moved into the districts). The decline in the number of cases persists. This finding is not compatible with any effect from MMR vaccine because uptake of MMR rose rapidly from it's introduction in 1988 and has since remained steady, while recorded cases of autism rose and fell over the same period (for reasons that are quite unclear).

Mr. BURTON. I want to thank the panel. We will now go to our questions.

Dr. Offit, you talk about collaboration, I guess, with the Merck Pharmaceutical Co.?

Dr. OFFIT. Yes. As I disclosed in my written report, I have been in collaboration with Merck and Company on the development of a rotavirus vaccine since 1992.

Mr. BURTON. Do you do any traveling around, speaking on behalf of Merck or Merck products?

Dr. OFFIT. I travel and speak about vaccines, and those talks are supported by unrestricted educational grants from either pharmaceutical companies or from universities.

Mr. BURTON. So they pay for your expenses and that sort of thing?

Dr. OFFIT. They have an interest in educating physicians about vaccines, and it is good that they do, because physicians need to be educated about vaccines.

Mr. BURTON. I understand. And they produce the MMR vaccine, don't they?

Dr. OFFIT. Yes, they do, yes.

Mr. BURTON. Thank you.

Dr. Taylor, in your Lancet paper, you omitted to mention the Catch-Up Campaign. That is the vaccination of children over 1 year of age when the vaccination was introduced. Yet you appear to have included these Catch-Up children in your analysis of the step-up hypothesis. So you consider that to be methodologically—do you think that is a correct analysis?

Dr. TAYLOR. Basically, that statement is not true, Mr. Chairman. We did include the children involved in the Catch-Up Campaign in our analysis, as is clearly stated. To suggest otherwise—and I suspect the suggestion comes from Mr. Wakefield—is malicious.

Mr. BURTON. Well, was it included—was it not omitted in the original paper that you submitted?

Dr. TAYLOR. No. All cases were included who received MMR vaccine. All cases—we will submit additional analysis with all cases who received any measles-containing vaccine——

Mr. BURTON. Didn't some of those 36 children receive the MMR vaccine after the——

Dr. TAYLOR. I think what you are referring to is the reply which we put to Mr. Wakefield's criticism of our paper in the Lancet. I have to say that his is the only criticism of our paper which we have received on a scientific basis. All other reports have been constructive and supportive.

Mr. BURTON. Well——

Dr. TAYLOR. What we looked for there were the children who had received MMR vaccine, which we had included in our analysis. There were 36 such children, and in 29 of them, there was evidence regarding when the parents became concerned about their child's development. In all cases, this was before they received the MMR vaccine.

Mr. BURTON. We have an epidemiologist in the audience, and—where is he?

Would you mind coming up? I would like to have you sworn in real quickly.

Dr. SPITZER. Yes.

[Witness sworn.]

Mr. BURTON. Thank you.

Can you explain the importance of properly counting these children born before 1988 who were given the Catch-Up vaccines?

STATEMENT OF DR. WALTER O. SPITZER, PROFESSOR EMERITUS OF EPIDEMIOLOGY, MCGILL UNIVERSITY, AND MEMBER, NATIONAL ACADEMY OF SCIENCE OF THE UNITED STATES, CORPUS CHRISTI, TX

Dr. SPITZER. Well, as implied by Professor——

Mr. WAXMAN. Point of order, Mr. Chairman. Point of order, if you will suspend your answer to that question. I want to make a point of order.

Mr. BURTON. The gentleman will state his point of order.

Mr. WAXMAN. The rules of this committee require that "Witnesses appearing before the committee shall, so far as practicable, submit written statements at least 24 hours before their appearance, and, when appearing in a nongovernmental capacity, provide a curriculum vitae and a listing of any Federal Government grants and contracts received in the previous fiscal year. Identification of witnesses are to be provided to members of the committee."

Suddenly, we have a witness being called forward, and Rule 2 says "Every member of the committee or the appropriate subcommittee, unless prevented by unusual circumstances, shall be provided with a memorandum at least 3 calendar days before each meeting or hearing explaining 1) the purpose of the meeting or the hearing, 2) the names, titles, background and reason for appearance of any witness. The ranking minority member shall be responsible for providing the same information on witnesses whom the minority requests."

Suddenly, we have a witness being called forward. We have all of these people testifying, and we have now a witness coming up—I do not know who he is. It just seems to me that this is in violation of the rules.

Mr. BURTON. I think as you were reading there, where there are "unusual circumstances"—and I believe you can go back and read that again—or whenever "practicable" was another term that was used in there—so the chair—excuse me, let us suspend for one moment. [Pause.]

Mr. WAXMAN. Mr. Chairman, if I might be heard——

Mr. BURTON. No——

Mr. WAXMAN [continuing]. And I am going to withdraw my point of order—but I do want to say that there are procedures for the conduct of hearings which provide for opportunities for all points of view to be expressed. And for a witness to be brought out of the audience because the witnesses before you did not give you testimony that fit with your preconceived theory seems to me to turn a congressional hearing more into a circus than a genuine fact-finding opportunity.

But I will not object if you want to call this witness. I do want to also point out that we have rules on the time allocated to members, and I would insist that that time be observed or that all members be given the same open-endedness that I see about to come in your questioning, because the clock that usually keeps time for our questioning has been deliberately stopped.

I will not object, but I do think it is inconsistent with the rules of this committee to bring witnesses out of the audience when you have a panel here that just testified, with whom we ought to pursue our questions.

Mr. BURTON. The parliamentarian has just informed me that where there are extenuating circumstances, the chair has the ability to bring a witness forward—and this is not the first time this has happened.

[Applause.]

Mr. BURTON. That is the first thing. The second thing is that this is one of the most important hearings I think we have had, because we are talking about an epidemic of autism that is taking place in this country, and if there is information that is being given to the committee that is going to be in the Congressional Record that is not accurate, it needs to be corrected as quickly as possible so the American people and people from around the world who may want to look at the record of this committee have the facts.

Now, if we have an epidemiologist here who has expertise about a report and can cite that information about this report where there might be an error, then we ought to correct it right now, instead of waiting until a report is filed, goes out to the American people, and then try to correct it where there might be a misunderstanding. So——

Mr. WAXMAN. Well, we do have an epidemiologist on this panel, and perhaps you ought to question her, or this other witness should have been asked to testify. No one would have objected to having anybody who had anything pertinent to say to us to have an opportunity to present what they have to say.

Mr. Chairman, let us proceed, and let us keep the rules on time, or acknowledge the open-endedness of questions, because we will have a lot of questions as well.

Mr. BURTON. Dr. Spitzer.

Dr. SPITZER. Very briefly, Congressman Waxman, your points are well-taken, and I respect them. I will say now to Professor Taylor that those additional cases in the Catch-Up Campaign may well have been included in the paper but were not clearly segregated or identified or enabled peers to evaluate the possible impact of including them or not, so the findings may have been misleading until we reanalyze them taking that into account.

Moreover, the use of the case series strategy of analysis is unconventional, not accepted by mainstream scientists, and leaves the paper at best as a hypothesis-generating study and not something with which he or anyone can categorically say this proves that there is no relationship. It just shows and emphasizes what he said himself, that we need to study it further.

So we have a compelling reason to have a blue panel, an international panel, to go back to that data base, look at the raw data, and be able to come up with a second assessment that is verifiable by the scientific community and the relevant community.

Thank you, Mr. Waxman, Mr. Chairman.

Mr. BURTON. Thank you very much.

Mr. TIERNEY. Point of order, Mr. Chairman.

Dr. TAYLOR. Mr. chairman, can I comment on that?

Mr. BURTON. Stop the clock.

The gentleman will state his point of order.

Mr. TIERNEY. Is Mr. Taylor going to be given an opportunity to respond at this point in time?

Dr. TAYLOR. May I comment?

Mr. TIERNEY. I think it might be helpful to those of us who are sort of surprised by this new witness. I would like to hear what Mr. Taylor has to say in response to that. I think it would be educational.

Mr. BURTON. I have no objection to him responding, but I have some more questions of Dr. Wakefield, so——

Mr. TIERNEY. Well, Mr. Chairman, my point of order is can we have them nearer in time to each other so we can get the full benefit of it, rather than go back and forth.

Mr. BURTON. I will yield to the gentleman next. He can have the time next, or Mr. Waxman can, and he can yield to Dr. Taylor.

Dr. Wakefield, would you come back up, please? Dr. Wakefield, would you clarify the difference of opinion that you have from your colleague?

Dr. Wakefield. My anxiety, Mr. Chairman, is that if you test a step-up hypothesis—that is, those children who should be the first to receive the vaccine at the age of 1 year, born in 1987, because the vaccine was introduced in the UK in 1988, and therefore they would have been 1 year old, then the take-off, if there were a relationship between MMR and the vaccine, should have occurred at that point.

The paper illustrated the point that the take-off occurred before those born in 1985 and 1986. What took place when the MMR was introduced was the Catch-Up Campaign, where all children of 1 to 4 years of age were targeted. It was an aggressive campaign—I know that, because one of the authors on the paper that we published in the Lancet was in charge of that campaign for Hackmey in Northeast London. If you give the vaccine to children over the age of 2, then it will cause the take-off to occur before 1987, and that is exactly what occurred.

Now, at the very least, those cases should have been mentioned, because the reviewers, in the absence of those data, cannot give a valid interpretation of the paper when they make a recommendation for it to be published or not, and they should have been excluded from the analysis so we could see how the graph looked without them, and that did not occur, and that is a major anxiety.

Mr. BURTON. Dr. Taylor, do you want to respond now?

Dr. TAYLOR. It does seem slightly surprising that at one moment, we are accused of excluding them and therefore that upsets the results, and now we are accused of including them, and that upsets the results.

I have to say the time relationships, the step-up part of our paper is the least important part of our findings. The direct findings, the time series analysis, is much more important, which is the direct evidence that the individual children did not develop symptoms of autism within various defined periods after they received the MMR vaccine.

If I could just comment on Dr. Spitzer's comment, he describes our analysis as unorthodox. We used the highest standards of epidemiological and statistical analysis in our handling of this data, and this data has been reviewed by numerous experts, both prior to publication and since.

Last week, our research was the basis of a detailed debate at the Royal Statistical Society, where there was no criticism of the statistical techniques that we used, and the conclusions of our paper were accepted by this very expert group.

The testimony which you received from Dr. Elizabeth Miller, who is an epidemiologist, and Dr. Patty Farrington, who is an expert statistician, is tabled for the committee's consideration.

Mr. BURTON. Would you mind, since there is a strong difference of opinion between you and Dr. Wakefield, and I presume some others, providing the data for your study to the committee, the complete data?

Dr. TAYLOR. I will have to take advice on that from both my colleagues and the others. I would be required to decide whether the committee is an appropriate body for this information, which was collected, as you know, by the Medicines Control Agency, which is a branch of the Department of Health in the UK. In principle, I have no problem, but in practice, I would need to check——

Mr. BURTON. Well, we would be very happy to write to the Department of Health in the UK and ask that you be able to release that information to the committee in total so that we could have somebody who is totally nonbiased, hopefully, on this issue to analyze it.

Dr. TAYLOR. Yes. I think it would need to be done by more than a selected statistician. If it is to be reanalyzed, it should be reanalyzed by independent individuals—which, of course, is the problem with much of Mr. Wakefield's research, that it has never been independently verified. No one anywhere in the world has been able to reproduce any of his studies, and it seems possible, and it is only going to be a matter of time before this most recent information is also found to be inadequate.

Mr. BURTON. Well, my time has expired, but let me just say that I believe that Dr. Wakefield and Professor O'Leary and others would be willing to give us the documentation in the study that they did, and we would like to have yours as well so we can look at all of that.

Mr. Waxman.

Mr. WAXMAN. Mr. Chairman, because I believe autism is such a serious problem, I am troubled by this hearing. This hearing was called and structured to establish a point of view, and it is the point of view of the chairman. The chairman believes a particular point of view, and that is the connection between autism and vaccinations.

You can look at it by the first panel, where we had five parents, all of whom believed the same thing that the chairman believed, and the way we just had the handling of the questions a minute ago.

What also bothered me was when we asked that we have the American Medical Association or the American Public Health Association or the National Network for Immunization Information or the former Secretary of HHS, Dr. Louis Sullivan—real experts in addition to those we have before us—we were told no, they cannot fit in.

I think hearings like this have a real danger because if you sensationalize the idea that there is a connection between immunization and autism, immunization rates will drop. That is what happened in Great Britain after Dr. Wakefield published his first study. Immunizations dropped. Autism rates did not drop, but measles rates increased.

I was impressed by the statement that we had a drop of just 10 percent in measles immunizations in 1990, and then we had 11,000 people hospitalized from measles. This can cause brain retardation and death. We know we can prevent that. Why should we then scare people about immunizations until we know the facts?

I fear that what we have in this hearing is a sensationalization by the chairman in order to get all these cameras to report to the American people that there is this connection because he believes it, and many other people believe it, and therefore a lot of others who watch this will think, "I will not immunize my children."

Dr. Wakefield came out with a report in England, and the first group that examined his claims was the Medical Research Council, which is the British equivalent of the NIH, and they found no evidence to indicate any link between the MMR vaccine and bowel disease and autism.

After they did their work, the Chief Medical Officer of the United Kingdom issued a letter to doctors in 1998, stating, "Based on the previous material that I have seen and on the opinion of experts present at the Medical Research Council, I have concluded there is no link between measles, measles vaccine, or MMR immunization," etc.

Then, the World Health Organization looked at his study, and they came up with the following statement: "Given our view, the previous scientific claims made by Dr. Wakefield and colleagues lack scientific credibility, and his present study does not meet the requirements for establishing such a causal relationship."

I do not know whether that is true or not, but that is what the scientists in England said when they evaluated it, as did Dr. Taylor when he evaluated Dr. Wakefield's study.

Now, Dr. Wakefield has testified he has some new information. Fine. Let us get the new information out there. Let us let the epidemiologists evaluate it. Let us let scientists explore where the truth may be. But to put this out in a congressional hearing and scare people from getting immunizations—we know that without immunizations, dreaded diseases will occur, deaths and mental retardation and disability will occur among our children, and we can prevent that.

What we do not know, and we have a lot of information to the contrary, is that autism will result from that immunization.

Dr. Taylor—well, let me ask Dr. Boyle. You are an epidemiologist. Suddenly, we had to pull out of the audience an epidemiologist. But you are an epidemiologist. What do you have to say about this debate that we are seeing back and forth? Have you evaluated any of this information that is now being presented as if it were fact?

Ms. BOYLE. I think that the scientific data currently does not show an association between the MMR vaccine and autism. We have heard from Dr. Taylor. We also know that there is a study in Sweden by Dr. Gilberg and associates, who have been monitoring—Sweden is actually the only country that has been monitoring the rate of autism over time—and they looked at pre-MMR immunizations and post-MMR immunizations and found no changes in the rates of autism.

Mr. WAXMAN. Well, I cannot tell you what is true or not, but I do not think our chairman can tell you what is true or not either, and I feel that when we had the hearings on whether there were campaign abuses by Democrats, a lot of people's reputations were ruined, and I thought the hearings were unfair. But those were political. The consequences of an unfair hearing on autism connected to vaccinations can cause people to die, and I worry about that, and I think we should get the facts before we make the assertions and not make the assertions and then throw out the witnesses who tell us information that does not fit those allegations.

I yield back the balance of my time.

Mr. BURTON. The gentleman's time has expired.

Does the gentlelady from Florida wish to question the panel?

Ms. ROS-LEHTINEN. Thank you so much, Mr. Chairman, and I thank you for holding this hearing.

Rather than asking questions, because I am needed for a caucus in my other subcommittee, I want to thank you, Mr. Chairman, for holding this important hearing and for highlighting the need for further research as we explore the possible causes, interventions, strategies, counseling and other services to help families who are living with autism. We need to keep in mind that a person with autism is indeed a person first and not a behavior.

These posters, which I would like to have the audience and the panelists see, show constituents from my Congressional District, Bonnie and Willis Flick, two beautiful children in my district who are living with autism, and, indeed, the whole family lives with autism.

Bonnie and Willis are fortunate to be able to afford treatment and therapy, but so many other families are not as fortunate.

So I thank you for the opportunity to hear from researchers and from parents and people who cope daily with this disease, and I commend you for your initiative, Mr. Chairman, in seeking answers to help those individuals with autism and for the opportunity to learn from experts and researchers.

I especially want to thank you for allowing Dr. Cathy Pratt, the director of the Indiana Resource Center for Autism to come today and share her expertise on what we as policymakers can do to help families deal with autism.

Approximately 50 percent of Florida's children with autism reside in my community in south Florida, so I am delighted to have you take this leadership role, Mr. Chairman, and have your committee address this issue so that 1 day, we can find prevention and methods and a cure to help us all cope with this rising curse of autism.

I thank you very much, Mr. Chairman.

Mr. BURTON. Will the gentlelady yield to me?

Ms. ROS-LEHTINEN. Yes, Mr. Chairman.

Mr. BURTON. Let me just ask Dr. Wakefield, because I want to conclude with this panel and move on—would you be willing to give us all of the information on your study so it can be reviewed?

Dr. WAKEFIELD. Certainly.

Mr. BURTON. You will?

Dr. WAKEFIELD. Yes.

Mr. BURTON. Thank you very much.

Professor O'Leary, would you be willing to give us all the information on your study so that we can review it?

Dr. O'LEARY. Yes, sir; no problem.

Mr. BURTON. I cannot hear you.

Dr. O'LEARY. Yes, sir.

Mr. BURTON. OK.

Dr. Singh, would you be willing to give us all the information on your study so we can review it thoroughly?

Mr. SINGH. Yes, absolutely, without any hesitation.

Mr. Chairman, if there is a moment, if I may have a chance, I would like to raise some interesting points later on.

Mr. BURTON. Yes, but just 1 second.

Mr. SINGH. Yes. Thank you very much.

Mr. BURTON. Now, then, Dr. Taylor, will you give us all the information on your study so we can review it along with the others?

Dr. TAYLOR. In principle, I have no problem, but I would need to discuss that with my employing authority, University College London, and with the Department of Health, who funded this study.

Mr. BURTON. Who funded your study, Dr. Wakefield?

Dr. WAKEFIELD. We did. We have a small charitable contribution, but——

Mr. BURTON. A charitable organization did; I see.

Dr. WAKEFIELD. We found it a little difficult to get funding——

Mr. BURTON. And yours was done by the Government?

Dr. TAYLOR. It was funded by the Medicine Control Agency, which is the body charged with responsibility for the safety of vaccines and other treatments.

Mr. BURTON. Well, I would be happy to work with the ranking Democrat, Mr. Waxman, to get an independent group of doctors/scientists that we mutually agree upon to review all of your work to come to some kind of a conclusion if that is possible.

So, since Dr. Wakefield and Professor O'Leary and Dr. Singh have all agreed, we would sure like to have yours, and I will be happy to write a letter, as I said before, to the authorities in England asking for your report, and hopefully, we will get that along with the others so we can review them side-by-side.

Mr. WAXMAN. Mr. Chairman, on that point—and I want to agree with you.

Mr. BURTON. Sure. Mr. Waxman.

Mr. WAXMAN. I drafted a letter, and I am going to share it with you, and I hope you will join with me on this letter to Secretary Shalala. We say in this letter: "Because of the vital public health importance of childhood immunization as well as the growing concerns over the prevalence of autism in the United States, we urge you to convene, under the auspices of the National Institutes of

Health, the Centers for Disease Control and Prevention, and the Food and Drug Administration, an expert panel of leading scientists and clinicians to review whether there is any causal association between vaccines and autism. Given the grave possibility that immunizations against life-threatening childhood diseases may decline is a result of unsubstantiated allegation of vaccine-induced autism, I would want her to act as expeditiously as possible."

Perhaps you will join me in this letter because I think the only proper thing to do is to get the experts to evaluate all of these conflicting claims. I would not want the American people as a result of this hearing to stop being immunized if these claims are not——

Mr. BURTON. Let me reclaim my time and say nor would I, but one of the concerns—the time is right there; it is on the clock—let me just say that the Department of Health and Human Services and Donna Shalala and the others have some very competent people over there. We have been checking into all the financial records of the people at FDA, HHS, and CDC, and we are finding that some of those people, even on the advisory panels, do have some possible financial conflicts, as was expressed in the New England Journal of Medicine just recently, on their front page.

As a result, I will join with you to get an independent panel to review all of these studies, but I want to make sure they are not controlled by the health agencies of this country that may have some people who have some possible conflicts of interest. It has already been expressed in the New England Journal of Medicine, and we believe that that also possibly exists with some of the agencies of our health services here in the United States. So I will join with you, and we will pick them together, and we will try to make sure that we have some people who are totally unbiased.

Mr. WAXMAN. Well, "independent" means no conflict of interest. I would not want a panel that had people with a conflict of interest, but I do want a panel of experts, and I think that the NIH and the CDC and the FDA can give us a panel that can do this evaluation. [Laughter.]

I do not know why some people find that amusing, but I think——

Mr. BURTON. So long as we find there is no conflict of interest, we would not have any problem with that.

Mr. Tierney.

Mr. TIERNEY. Thank you, Mr. Chairman.

I have to say that I am a bit disturbed with the nature of this hearing and the direction that it has gone, only because I have a considerable number of people in my district who have not only children with autism, and they deal with it every day, but we have a number of institutions that have been working hard to give people the kind of support they need to deal with this situation, and I find this hearing taking on a lot different tone than a hearing that would like to look at some solutions and work together in a cooperative way to find out just what we can do.

I do note that Representative Michael Bilirakis from Florida has some legislation filed, and one of the provisions would authorize funding for the NIH to establish Centers of Excellence that would conduct basic and clinical research into the causes, diagnosis, detection, prevention and treatment of autism. I congratulate the members of this panel who are cosponsors on that legislation and hope that that is the direction in which we will proceed, because I think we need to find out what the causes are.

First, Dr. Boyle, you are an epidemiologist. Given your background, have you examined the evidence that autism is increasing in the United States?

Ms. BOYLE. We do know that the rates of autism appear to be higher than previously thought. As I said in my testimony, they range from 10 to 15 per 10,000. But that is really from studies from other countries. We have not had prevalence studies conducted in the United States. There were two done in the eighties that found very low rates, with perhaps methodologic reasons for that.

At CDC, we have begun to develop a monitoring program at CDC which is only for the Atlanta area. We have our first year of data collected, and we are in the process of reviewing the information on the children with autism, and we hope to have a rate fairly soon. And we would like to see similar activities in many other locations. We have a wonderful model on birth defects. They are many years ahead of us in terms of trying to understand the causes of birth defects, and there are about 35 States that monitor birth defects on an ongoing basis. That does not happen for developmental disabilities, and we need to make that happen.

Mr. TIERNEY. There are people in my district, particularly in the Merrimac Valley area, who seem to have at least acknowledged an increased number of reported cases, if not of autism itself, of one of the related diagnoses. Have you heard of——

Ms. BOYLE. It is a difficult issue because the diagnosis for autism has changed considerably. The first studies were based on fairly narrow criteria from the way it was originally described. The more recent studies have actually used criteria that are much broader, and there is increased recognition. So we really do not know. There have been a number of investigators who have tried to see whether the increase in rates over time, or the higher rates in more recent years, is really due to a real increase or sort of a redefinition and better awareness. It is not an easy question to answer.

Mr. TIERNEY. I bring that up only because in one instance, at least, a group of very active parents of children with autism worked with the school system and some other researchers and heightened the awareness of identification and found a marked increase in the number of cases that were beginning to be identified in the area, so people had not really appreciated these symptoms, including some doctors, pediatricians, who looked at it.

Does that sound right to you?

Ms. BOYLE. The one study that has addressed this is the study by Gilberg which I mentioned earlier, which looked at trends over time. If you look at the range of functioning of those children over time, it appeared that the increase was in children who were higher-functioning as well as children who were lower-functioning. So the classic group seemed to remain constant. Now, why that is happening, we do not know. That is what we hope to do the research to understand.

Mr. TIERNEY. Well, I agree that we ought to do this research and do it soon. I am a little bit concerned about what might be the message taken from this hearing by people and what we want to take on this.

Dr. Boyle, if you had young children today, would you vaccinate them?

Ms. BOYLE. I do have children, and they are both fully vaccinated, and I would vaccinate them again.

Mr. TIERNEY. Dr. Offit, how about you?

Dr. OFFIT. Yes. I have a 7-year-old son, Will, and a 5-year-old daughter, Emily, and they are both fully vaccinated.

Mr. TIERNEY. And you would do it again?

Dr. OFFIT. Of course. I want them to be protected against the viruses and bacteria that can cause serious disability and death. I am fortunate, actually—I was a little boy in the early 1950's, and when I was a little boy, there were four vaccines—diphtheria, pertussis, tetanus and smallpox. I was fortunate that I was not killed by measles or paralyzed by polio. My son, hopefully, did not have to be as lucky, but hopefully, as we move into the 21st century and can develop vaccines against respiratory virus and para flu, children will not have to die from those diseases.

Mr. TIERNEY. Dr. Boyle, you wanted to add something.

Ms. BOYLE. I did want to mention one thing. We do monitor the trend of other serious developmental disabilities in Atlanta, and just based on my own experience over the last 10 or 15 years, we used to see children who were deaf due to congenital rubella or who had mental retardation due to hemophilus influenza Type B. We no longer see those children in our program.

Mr. BURTON. The gentleman's time has expired.

Mr. TIERNEY. Thank you, Mr. Chairman.

Mr. BURTON. I just have a few more questions, and then we will go to the next panel—I think Mr. Waxman has a few as well.

Dr. Boyle, why did the CDC ignore the pleas of the parents of Brick Township when they begged CDC to look at the vaccine issue?

Ms. BOYLE. Actually, the study of Brick Township is sort of our first step, which is to look at the prevalence of——

Mr. BURTON. Did you check into the vaccine issue, though? The parents there wanted the vaccines looked into as well. Did CDC——

Ms. BOYLE. The concern with the parents from Brick Township in a number of meetings that we had with parents was related to environmental concerns.

Mr. BURTON. They did not——

Ms. BOYLE. We have been working with the Agency for Toxic Substances and Disease Registration——

Mr. BURTON. But didn't they also ask that the vaccines that had been given to their children also be investigated?

Ms. BOYLE. That is not my understanding. My understanding is that their initial concern was to answer the question, is the rate of autism in their community higher than what they thought——

Mr. BURTON. Well, the information that we have is that the parents of Brick Township were very adamant that they wanted the vaccines checked because so many of their children had become autistic. And evidently, that is not one of the things that CDC is looking into, and I would like to pose the question to you and have you answer it in writing—why? Why didn't CDC include as one of the things they were investigating the possibility that some of these vaccinations may have caused the autism increase? Would you check that out and let me know?

Ms. BOYLE. I would be happy to.

Mr. BURTON. OK.

[The information referred to follows:]

Prevalence of Autism in Brick Township, New Jersey, 1998:Community Report

Centers for Disease Control and Prevention
April 2000

Return to Table of Contents

EXECUTIVE SUMMARY

Background

A citizen's group in Brick Township, New Jersey contacted the New Jersey Department of Health and Senior Services (DHSS) in late 1997 with concerns about an apparently larger than expected number of children with autism in Brick Township. Because of the complexity of the disorder and the citizens' concern that environmental factors might play a role, the New Jersey DHSS, U.S. Senator Robert Torricelli, and U.S. Representative Christopher Smith contacted the Centers for Disease Control and Prevention (CDC) and the Agency for Toxic Substances and Disease Registry (ATSDR) for assistance. In response, a four-part plan was developed, including a prevalence investigation, a literature review of environmental factors associated with autism, an investigation of environmental pathways for human exposure in the community, and community education and involvement activities. This report presents the results of the prevalence investigation.

Methods

The objective of the prevalence investigation was to determine the prevalence rate of autism in children aged 3-10 years who were living in Brick Township in 1998. Investigators used a two-phase approach. Phase I involved identifying all children whose condition might meet the case definition for autism by reviewing records at schools, service providers (physicians or programs for children with autism) and from names provided by the citizen's group. Phase II was to verify case status through an examination by a developmental pediatrician, using the Autism Diagnostic Observation Schedule-G (a scientifically well-established tool for diagnosing autism) in addition to standard clinical procedures. Autism included the spectrum of disorders defined by the American Psychiatric Associations's Diagnostic and Statistical Manual--Fourth Revision (DSM-IV), i.e., autistic disorder, Asperger's disorder, and pervasive developmental disorder--not otherwise specified (PDD-NOS). In order to determine the prevalence rate, it was necessary to estimate the number of children aged 3-10 years in Brick Township in 1998.

Results

Phase I of the investigation identified 75 children with possible autism. In Phase II, 60 children were found to meet the DSM-IV criteria for an autism spectrum disorder (ASD). The prevalence rate of ASD was 6.7 cases per 1,000 children (95% CI- 5.1-8.7). For the subset of 36 children whose condition met the diagnosis for autistic disorder, the prevalence was 4.0 cases per 1,000 children (95% CI = 2.8-5.6). The male-to-female prevalence ratios were 2.2 and 3.7 for autistic disorder and PDD-NOS, respectively. Sixty-three percent of the children with autistic disorder had an IQ score of less than or equal to 70 (i.e., mental retardation). Of children with a known birth residence, 64% were born in Brick Township. Seven children were reported to have a brother or sister who also had an ASD.

Conclusions

The rate of autistic disorder and ASD in Brick Township were high relative to previously published studies from other countries. There are no recent prevalence studies of autism in the United States. However, there are a few very recent studies from other countries that have yielded similar rates. These studies, like the Brick Township investigation, tended to use relatively intense case-finding methods.

The well described epidemiologic characteristics of children with ASD in Brick Township-- the predominance in males and the high proportion of children with IQ of 70 or less -- were observed in the Brick Township population, which provides support for the appropriateness of our study methods.

Whether the Brick Township rates are higher than expected is difficult to answer because of the uncertainty about the true rate of autism. Recent higher prevalence rates found in other countries along with the increase in the number of children seen by service providers in the United States, is believed to be due in part to the broadening of the diagnostic criteria and improved recognition.

To help with the interpretation of the rate of autism in Brick Township, and rates in other communities, we need comparable data on the prevalence of autism in several large and diverse populations in the United States. Studies examining the role of genetic, infectious, immunologic, and environmental factors in the occurrence of autism are also needed.

Return to Table of Contents

Prevalence of Autism in Brick Township, New Jersey, 1998:Community Report

Centers for Disease Control and Prevention
April 2000

Return to Table of Contents

Background

Brick Township, New Jersey, a town of about 77,000 residents, is located approximately 60 miles north of Atlantic City, just a few minutes from the Atlantic coast. In late 1997, a citizens' group in Brick Township, Parents of Special Services and Education (POSSE) contacted the New Jersey Department of Health and Senior Services (DHSS) with the results of a survey they had conducted on the number of children in their community with autism. The results of this survey suggested that the rate of autism among Brick Township children could be several times higher than expected based on prevalence rates for the disorder. In early 1998, the Centers for Disease Control and Prevention (CDC) and the Agency for Toxic Substances and Disease Registry (ATSDR) were contacted by the New Jersey DHSS, U.S. Senator Robert Torricelli, and Representative Christopher Smith about the possibility of federal assistance in addressing the concerns of the citizens of Brick Township. CDC assistance was requested because of the complexity of investigating a disorder such as autism, in which the diagnosis is based solely on the behavioral characteristics of the child, and CDC was developing epidemiologic methods to address the unique challenges of autism. ATSDR's expertise was requested because of a concern by the community that the apparent increase in autism might be caused by environmental factors.

In response to the requests for federal assistance, a four-part Health Action Plan for Brick Township was developed which included: (1) a prevalence investigation of autism; (2) a review of the literature on the association between chemical contaminants and autism; (3) an investigation of environmental pathways for human exposure in Brick Township; and (4) community involvement and health education activities. This report presents the results of the Brick Township autism prevalence component.

[Return to Table of Contents]

Methods

The population for the prevalence investigation was children aged 3 through 10 years whose parents resided in Brick Township, New Jersey, at any time during 1998. The age range was chosen to be analogous with the ages of children identified in CDC's Atlanta-based surveillance program for autism and other developmental disabilities, the only other current U.S. population-based study of autism.

Children with autism in Brick Township were identified using a two-phase process. In *Phase 1*, all children who met the age, study year, and parental residence requirements with possible autism were identified through a review of school, medical, and other source records. In *Phase 2*, clinicians with training and experience in diagnosing autism confirmed the diagnosis in children identified through *Phase* 1.

Case definition: The case definition included children with an autism spectrum disorder (ASD). This includes the diagnoses of autistic disorder, pervasive developmental disorder--not otherwise specified (PDD-NOS), and Asperger's disorder, based on the American Psychiatric Association's Diagnostic and Statistical Manual--Fourth Edition (DSM-IV) criteria. The case definition did not include children with childhood disintegrative disorder or Rett Syndrome. (See Appendix for DSM-IV criteria.)

[Return to Table of Contents]

Phase 1--Identification of children in Brick Township with a possible ASD.

Three sources were used to identify children with a possible ASD: 1) school records maintained by Brick Township Schools, Department of Special Services; 2) records of private physicians (i.e., neurodevelopmental pediatricians and pediatric neurologists) and private schools or programs that specialize in diagnosing or treating ASD in children; and 3) lists of children with a possible ASD maintained by POSSE and children whose parents contacted CDC directly .

To identify children whose condition might meet the prevalence case definition from special education records in the Brick Township schools, a developmental psychologist reviewed records of all children who received special education services in 1998. This review included records of children who were receiving services in private schools (for whom the services were paid by the Brick Township school system) and children who were evaluated for services but did not meet eligibility requirements for services. Children were identified as possible cases if their special education classification was an ASD, their record described behaviors consistent with diagnostic criteria for ASD, or another indication that an ASD may be present (i.e., a sibling with the disorder).

To identify children with ASD from private clinicians and private schools or other programs that provide services to children with autism, a list of such sources was developed through input from parents, school administrators, parent organizations (i.e., POSSE and the Center for Outreach Services for the Autism Community), the Ocean County Health Department, and area phone books. Fifteen private schools, four psychiatric facilities that provide inpatient and/or outpatient services for children with autism and other psychiatric disorders, three child psychiatrists, four pediatric neurology practices, and one general pediatrician were identified as possible sources. CDC investigators contacted these potential sources by telephone to determine whether they provided services to any children from Brick Township. Several schools provided services for Brick Township children with autism, however, these children already had been identified from the special education files maintained by the Brick Township schools. The psychiatric facilities all reported that in 1998 they served no children with autism from Brick Township. Of the clinicians, three pediatric neurologists were identified who provided diagnosis and treatment to children from Brick Township in 1998 and who allowed access to their records. The fourth pediatric neurologist reported having seen no children with an ASD from Brick Township. A review of the files from the general pediatrician indicated that we had already identified all children with autism in that practice. We were unable to obtain any information from the three child psychiatrists. Although it is unknown whether additional children would have been identified from the three child psychiatrists, only one of these clinicians was named in the record review at the school and other sources.

The final source for case identification included the lists of children with possible autism maintained by POSSE (after permission was obtained from the parents to forward their names to CDC) and parents who contacted CDC directly after learning of the investigation.

For each child identified as a possible case-child from the schools, physician offices, and the parent lists or inquiries, a team of two CDC research assistants (who specialized in abstracting psychological and medical reports for children with developmental disabilities) abstracted information from the records onto an abstract form developed by CDC investigators for use in its Atlanta-based autism surveillance program. Information abstracted from the records included demographic factors, descriptions of behaviors consistent with the DSM-IV diagnostic criteria for an ASD, standardized testing results (e.g., IQ testing), special education eligibility/classification, and selected medical tests and procedures (e.g., genetic testing results, metabolic screening results).

[Return to Table of Contents]

Phase 2 – Clinical assessment for autism.

Families of children who were identified in *Phase 1* were invited to participate in a clinical assessment. For logistical reasons, the six children who were identified from physician offices only were not invited to participate in the clinical assessment. The purpose of the clinical assessment was to use a standardized instrument in applying the DSM-IV criteria for ASD in children identified in *Phase 1*. The clinical examination also afforded the opportunity to obtain consistent demographic and medical history information. All clinical assessments were conducted at the Ocean County Health Department after written informed consent was obtained from parents of all participating children.

The clinical evaluation was conducted by a developmental pediatrician with extensive experience in diagnosing and treating children with ASD. The clinical evaluation included a medical, developmental, and behavioral history; a standard physical and neurologic examination; and front and side view photographs, that were subsequently evaluated by a geneticist. In addition to these standard clinical procedures, the Autism Diagnostic Observation Schedule-G (ADOS-G) was administered. The ADOS-G is a semistructured observational assessment that includes activities to evaluate the child's functioning in the critical areas of social interactions, communication, and repetitive or restrictive behaviors. The ADOS-G allows for DSM-IV diagnoses within the autism spectrum, with threshold scores for autistic disorder (Lord, 1998; Lord & Risi, 1998; Lord et al., 1989). The developmental pediatrician received special training in the administration of the ADOS-G and the reliability of her diagnosis was monitored in accordance with recommended guidelines for this measure.

In addition to the clinical evaluation by the developmental pediatrician, a battery of tests was administered by a developmental psychologist to assess the intellectual, language, spatial-cognitive, and adaptive functioning of each child. Three instruments were used: the Differential Abilities Scale (a test of general intelligence, Elliott, 1990); the Developmental Test of Visual-Motor Integration (which assesses spatial-cognitive ability, Berry, 1997); and the Vineland Adaptive Behavior Scales (which measures application of cognitive ability to functioning in everyday life, Sparrow et al., 1984). Each of the tests is standardized for administration and scored to a mean of 100 and standard deviation of 15. Scores below 70 (or two standard deviations below the mean) indicate significant delay or impairment.

Case Status. Case status was determined using all information for each child. For the children who participated in the clinical examination, the diagnosis of ASD was determined primarily from the ADOS-G results, although the developmental history of the child was also considered. However, history and functioning information altered the final case status based on the ADOS-G results in only a few instances. For all other children identified as possible case-children (i.e., children who were invited but did not participate in the clinical assessment phase and children identified from physician offices only), the clinicians determined case status on the basis of a review of all the abstracted diagnostic information for each child. Behaviors described in these abstracted records that corresponded to each of the DSM-IV criteria for autistic disorder were recorded by the clinicians onto an abstract form. Following DSM-IV criteria, the number and pattern of behaviors were used to determine whether the child was within the autism spectrum and whether the child's disorder met the full diagnostic criteria for autistic disorder.

[Return to Table of Contents]

Calculation of Prevalence Rates The prevalence rates of all ASD (autistic disorder, PDD-NOS, and Asperger's disorder), autistic disorder alone, and other spectrum disorders (i.e., PDD-NOS and Asperger's disorder combined) were calculated for children aged 3 years through 10 years, who resided in Brick Township at any time during 1998. The numerator of the rate is the number of children identified by the clinical exam or clinical record review (when exams were not done) as meeting the case definition for one of these conditions. The denominator is the estimated number of children aged 3 through10 years whose parents resided in Brick Township in 1998.

Because the exact number of 3- to10- year old children living in Brick Township in 1998 was not available, we estimated the denominator by adjusting the 1990 census count of 7,117 by a 25% inflation factor. This inflation factor was equivalent to the increase observed in the Brick Township student population for grades K through 5 in the school years 1989-90 and 1998-99, which were provided by the Brick Township Public Schools. Using this inflation factor, the estimated number of children aged 3 - 10 years in Brick Township in 1998 was 8,896 (4,364 girls and 4,532 boys).

Statistical precision of the prevalence rates were assessed by computing 95% confidence intervals, which indicate that 95% of the time the interval will include the true rate. Confidence intervals were used to compare prevalence rates within Brick Township, such as between younger and older children, and to compare the prevalence in Brick Township with that found in other studies. Confidence intervals that do not overlap provide guidance that the rates are statistically different from one another.

For the most part, the analyses include information about all children identified with an ASD in Brick Township, with the sample restricted for a few analyses only to children who participated in the *Phase 2* clinical assessment. Findings are presented for all children within the autism spectrum as well as separately for children whose disorder met the diagnostic criteria for autistic disorder and for children who had the other spectrum disorders (PDD-NOS/Asperger's disorder).

[Return to Table of Contents]

Results

Seventy-five children were identified as possible case-children in *Phase 1* of the investigation (Table 1). Most (83%) were identified at more than one source. Of the 75 possible case-children, 53 participated in the clinical examination, and 22 were evaluated solely on the basis of diagnostic information included in school and physician records. Sixty of the 75 potential case-children met the DSM-IV criteria for an ASD; 36 of these children met the criteria for autistic disorder. Fifteen children identified as possible case-children in *Phase 1* did not meet the ASD diagnostic criteria; these children had a number of other developmental disorders, such as attention deficit hyperactivity disorder, mental retardation, or a speech disorder. The following results are based on the 60 children whose conditions met the DSM-IV criteria for an ASD

The overall and age-specific prevalence rates in Brick Township for autistic disorder, other spectrum disorders (PDD-NOS/Asperger's disorder), and all ASDs combined are presented in Table 2. Age-specific rates were based on the child's attained age in 1998. The overall rate of autistic disorder is 4.0 cases per 1,000 children aged 3-10 years, with a 95% confidence interval (CI) ranging from 2.8 to 5.6. The overall rate for children meeting the criteria for other spectrum disorders was 2.7 (95% CI = 1.7-4.0). Finally, the overall rate of ASD was 6.7 cases per 1,000 children aged 3-10 years (95% CI = 5.1-8.7). Age-specific prevalence rates of ASD or autistic disorder in children 3-5 years old did not differ significantly from those among children 6-10 years in 1998, although the tendency was for lower rates prevailing among the older aged children.

Forty-four (73%) of the 60 children with ASD were boys (Table 3). The male-to-female prevalence rate ratio was higher for children with PDD-NOS/Asperger's disorder than for children with autistic disorder, 3.7 and 2.2, respectively.

The racial/ethnic distribution of children with ASD was 89% white non-Hispanic, 4% Hispanic, 4% other races, and 3% unknown. This distribution is comparable to Brick Township--94% white non-Hispanic, 4% Hispanic, and 2% other races. Of the 60 children with ASD, maternal residence at time of the child's birth was obtained from school or other sources (e.g., birth certificates) for 56 (93%) of the children. Of the 56 children with known birth residence, 36 (64%) were born in Brick Township, and 20 (36%) had a maternal residence other than Brick. One child with ASD, born outside Brick Township, was adopted.

In addition to the 43 case-children who participated in the clinical exam, IQ information was available for two of the 17 children with only record information, and these children are included in the IQ analysis. The mean IQ score for children with ASD was 72 (range 45 to 118); 21 (47%) children had IQ scores less than or equal to 70. Of children who met the diagnostic criteria for autistic disorder, 50% had an IQ score of less than or equal to 70, and 40% of those with PDD-NOS/Asperger's disorder fell in this range (Table 4). Four children with autistic disorder could not complete the IQ testing because of limited language ability and/or cooperation. All four of these children were considered by the developmental psychologist to be functioning in the moderate to severe range of mental retardation; the corresponding Vineland standard scores for each child was less than 50, indicating moderate to severe deficits in skills of daily living. Including these four children in the less than or equal to 70 IQ group would result in 63% of the children with autistic disorder functioning in the range of mental retardation.

Parents were asked during the clinical assessment whether their child had experienced any loss of acquired skills before the diagnosis of ASD. Ten of the 43 children who participated in the exams, all in the autistic disorder category, were reported by their parents to have lost skills. The earliest age of skill loss was reported as 12 months for four children, 13 months for one child, 15 months for two children, and 18 months for three children. For the 17 children with record information only, no information in their medical or school records indicated a loss of skills.

Seven children from four families were reported by their parents as having a sibling with an ASD (Table 5). For three of these sibling pairs, both children met the age criteria to be included in the prevalence investigation. There were a total of 81 siblings in the investigation, which yields a sibling rate of ASD of 4.9%. In addition, six children were reported to have one or more siblings with a developmental disability other than an ASD, primarily attention deficit hyperactivity disorder or speech/language disorders.

Five (8.6%) of the 60 children had specific medical conditions that have been found in other studies to be associated with autism. These conditions were seizure disorder (two children), fragile X syndrome (two children), and a genetic translocation (one child). A clinical geneticist at CDC reviewed photographs and videotapes the facial features of 43 children who participated in the clinical evaluation and indicated that none had a major, recognizable syndrome. A few children had several dysmorphic features, but there was no common facial appearance.

[Return to Table of Contents]

Discussion

The rate of autistic disorder in Brick Township was 4.0 per 1,000 children. The rate for the spectrum of autism disorders obtained in this investigation was 6.7 per 1,000 children. These rates are higher than previously published rates. However, there is much controversy about the actual rate of autism. Considerable debate has focused on the actual prevalence of autism and whether the prevalence has increased during the past 20-30 years (Fombonne, 1996; 1999; Gillberg & Wing, 1999). Nearly all recent studies (Table 6) suggest that the prevalence of autism is considerably higher than the rates of 0.4 to 0.5 per 1,000 that were originally described. These early rates were based on narrowly defined criteria for autism that included two essential features--a profound lack of affective contact and elaborate repetitive and ritualistic behaviors (Kanner & Eisenberg, 1956). More recent diagnostic criteria for autism, based on the DSM-IV (1984) or the *International Classification of Diseases Tenth Revision* (ICD-10, 1992), are considerably broader incorporating the clinical recognition that the hallmark features of autism--impaired social interactions, inability to communicate, and repetitive or restrictive behaviors--can occur in a wide range of severity levels with several different manifestations (Wing, 1993; Filipek, et al., 1999). Recent reviews of the prevalence of autism (Fombonne, 1999; Gillberg & Wing, 1999) suggest that a conservative estimate of the prevalence of autistic disorder from studies published in the 1990's is about 1 per 1,000 children. For the entire spectrum of autistic disorders, the rate of 2 per 1,000 that was obtained by Wing and Gould (1979) is cited most often. However, a few recent studies have shown rates that are considerably higher than the above estimates. Specifically, studies conducted in Japan and Sweden showed rates of autism ranging from 2.1 to 6.0 per 1,000 children (Honda et al, 1996; Arvidsson et al., 1997; Kadesjo and Gillberg, 1999). Although each of these studies included relatively small populations, which would have facilitated more intensive case finding methods, the small sample sizes also resulted in statistically unstable prevalence rates as reflected by wide confidence intervals. However, a study recently completed in the United Kingdom, with a considerably larger population, reported a provisional rate of 3.1 per 1,000 children for autistic disorder and 5.8 per 1,000 children for ASD (Baird et al., in press). One reason for the higher rates in these studies may be their more intensive case-finding methods that included screening the entire population. As discussed below, intense case finding activities may have contributed to the high rate in Brick Township.

Another important point to consider when interpreting the rate found in Brick Township is the lack of U.S. data on the prevalence of autism, although there is no reason to believe that the rate in U.S. populations should differ appreciably from other population groups. The data used by Gillberg and Wing (1979) to derive their estimate of 1 per 1,000 for the prevalence of autism is based on studies conducted outside of the United States. The two U.S. studies that satisfied the criteria to be included in the review--population-based screening followed by a clinical evaluation--obtained rates of 0.3 per 1,000 (Burd et al., 1987; Ritvo, et al, 1989) and are considered outliers by most investigators (Gillberg & Wing, 1999). The low rates in these U.S. studies probably result from their exclusive reliance on referred cases from sources that provided services to children with autism, rather than actively reviewing all potential source records as in the Brick Township investigation.

Other U.S. data sources seem to support the idea that the prevalence of autism is higher than previously thought, although how much higher is still uncertain. A recent report released by the California Department of Developmental Services (DDS) showed a large increase from 1987 to 1998 in the number of children with autism for whom the DDS provided services. We estimated a prevalence rate from the California DDS data of 1.5 per 1,000 4-9 year old children (95% CI=1.45-1.54) in 1998 by using the number of children aged 4-9 years receiving DDS services for autism in 1998 as the numerator and the U.S. census estimate of the number of children in this age range living in California in 1998 as the denominator. This rate is probably an underestimate because this service system is unlikely to identify all children with autism. CDC has recently completed data collection for a large prevalence study in metropolitan Atlanta. Although case review and data analysis are ongoing, provisional rates of autistic disorder based on the number of cases reviewed (40% of total), and assuming a similar rate of case confirmation for the remainder, range from 2 to 3 per 1,000 3- to 10-year-old children. The combination of the Atlanta and California data suggest that the rate of autistic disorder in the United States is substantially higher than the 1 per 1,000 estimate of Gillberg and Wing (1999), although how much higher and how the rates vary across different subpopulations is yet to be determined.

Another data source that might add some perspective to the Brick Township rates is the New Jersey special education data for autism. The percentage of children provided special education services by Brick Township was not unusual compared to other towns in New Jersey during 1997. In the annual reporting for federal funding under the Individuals with Disabilities Education Act, there were over 100 towns in New Jersey that reported a higher percentage of children in autism special education classes than reported in Brick Township (Factor-Litvak, personal communication). However, the special education data have to be viewed with caution because school placement is based on the educational needs of the child rather than exclusively on underlying diagnosis, and classification practices may vary among school systems. For example, in Brick Township, only 50% of children with an ASD and 66% of those with autistic disorder had autism listed as their special education designation for services.

Differences in study methods may account for much of the variability in autism prevalence rates (Fombonne, 1996; 1999; Gillberg & Wing, 1999; Wing, 1993; Bryson & Smith, 1998). We mentioned previously that other studies with higher rates tended to have more intense case finding methods. In Brick Township, a number of factors contributed to the intensity of case finding. First, the relatively small size of the target population allowed CDC investigators, parents, and professionals in the community to be especially thorough in identifying and reviewing potential case sources. Second, the local school system was fully cooperative with investigators, which facilitated the identification of all children receiving special education services, including newly referred children. Third, the well-organized citizen groups resulted in an acute awareness of the features of autism in the community among both parents and professional groups. Finally, the intense media coverage that followed the initial report of a possibly large number of children with autism in Brick Township undoubtedly led to a greater awareness of the condition by parents and professionals.

We found 1.5 times more children with autistic disorder than with other ASDs. A recent review suggested just the opposite–a higher prevalence of other spectrum disorders than autistic disorder (Fombonne, 1998). There are several possible explanations for the discrepant findings. One possibility is the instrument used to guide the clinician's diagnosis of autism, the ADOS-G, is limited in its ability to discriminate autistic disorder from PDD-NOS (Lord, 1998). However, the mean scores were similar for functioning assessed by the ADOS-G (i.e., social, communication and repetitive behaviors domains) to the mean values from the sample used to develop the norms for the ADOS-G. Such similarity suggests we did not overdiagnose autistic disorder relative to the normative data. Another possible explanation is that our method of case identification was not good at identifying children with other spectrum disorders. Our method of case finding assumed that the autistic behaviors of children would be recognized and/or described previously by someone--an educator, parent or clinician–even in the absence of a formal autism diagnosis or classification. Some children with PDD-NOS or Asperger's disorder may function well in the community and therefore may have been missed by our case-finding process.

We observed several well-established epidemiologic characteristics of children with autism in this investigation, although the strength of the associations were perhaps less remarkable than in most previous studies. These characteristics included the predominance of males and the high proportion of children with co-existing mental retardation. The male-to-female ratios found in other studies have ranged from about 2:1 to 4:1 with a few exceptions of very high ratios (see Table 6). Thus, the 2.2 male-to-female prevalence ratio for autistic disorder observed in Brick Township is at the lower end of the range found in other studies. The higher male-to-female ratio for PDD-NOS/Asperger's disorder than for autistic disorder seems unusual, however, less is know about epidemiologic characteristics of this clinical entity and as noted, we may have missed children with other spectrum disorders. Similarly, we found about two thirds of the children with autistic disorder and slightly less that half the children with PDD-NOS had co-existing mental retardation. The prevalence of co-existing mental retardation in prior studies ranged from 44% to 100%, with the majority of studies in the 60%- 80% range. The proportion of case-children in Brick Township with mental retardation was at the lower end of this range. Possible explanations included the intelligence test used, the Differential Abilities Scale, which is a preferred test for children with autism because it minimizes the level of verbal abilities needed to complete the tasks in comparison to other standardized IQ tests (Tager-Flusberg and Joseph, 1999). Also, the growing availability of early intervention services may impact the level of functioning for the group of children from this community. Finally, if children without IQ information were lower functioning than children for whom IQ information was available, the proportion with mental retardation would have been higher.

Epilepsy has been found in other investigations as the second most common co-existing medical condition among children with autism, occurring in up to 25% of case children; other medical conditions occur much less frequently (Fombonne et al., 1997; Gillberg et al., 1994; Sponheim & Skejeldal, 1998). Associated medical conditions of any type were reported in just five (8%) the case children in Brick Township. Only two of these children (3%) were reported to have epilepsy.

The strong genetic component of autism has been well described in family and twin studies (Szatmari, 1998; Spiker, 1999). In this investigation, 7% of the 57 families had more than one child with an ASD; the rate of ASD in siblings was 5%. Genetic family studies had found rates of ASD of 5-6% in siblings (Szatmari et al., 1998), suggesting that Brick Township is within the range of what has been observed previously.

While we obtained permission to review records from most potential case sources, there were three physicians identified as possible sources who elected not to participate. Although the names of only one of these physicians was noted in the chart review at other sources, it is unknown whether additional case children would have been identified from their practices. This might be especially true for higher functioning children who were not known to other sources.

One possible explanation for a high rate of autism in Brick Township is that families with children with already diagnosed ASD were more likely to have moved into Brick Township than other families. Although we did not have specific information about the changes in the Brick Township population over time, we do know that about one third of the families with children with ASD who were included in the study moved into Brick Township sometime after their child's birth. This rate of in-migration is comparable to the rate of growth experienced by the Brick Township schools where the elementary school population increased 25% in the 9-year interval from 1990 to 1998.

[Return to Table of Contents]

Conclusions

Our investigation found high rates of autistic disorder and ASD in Brick Township relative to rates from previously published studies. The rates for the majority of recent studies are several fold lower than the rate in Brick Township. However, a few, very recent studies yield rates close to those in Brick Township. These studies, like the Brick Township investigation, tended to use relatively intense case-finding methods. In Brick Township, the relatively small size of the target population; the heightened awareness of parents, teachers, and clinicians; and the full cooperation of most of the service providers allowed for thorough case-finding. The use of the ADOS-G may have contributed to the high rate of autistic disorder because children with more subtle signs of an ASD may have been included as cases. At the same time, comparability between epidemiologic characteristics of children with ASD in Brick Township and those in previous studies attest to the validity of our methods.

Although progress has been made in understanding this complex neurobehavioral disorder, a great deal of research still remains. The important population-based research that will provide full understanding of the magnitude of this important public health problem and identification of potential risk factors has only recently begun in the United States. To best interpret the rate of autism in Brick Township, we need comparable data on the prevalence of autism from a number of large and diverse populations in the United States. Such studies must use standardized case-finding methods and similar diagnostic tools to enable comparisons of rates across different geographic areas and across other population characteristics, and to identify potential causes for autism.

Subsequent steps may include conducting a large community-based case-control study of autism in Brick Township and in several other communities in New Jersey. This investigation could include a prevalence phase, to compare the prevalence rates of autism in Brick Township and surrounding communities with other areas in New Jersey. An analytic phase could examine the roles of various genetic, infectious, immunologic, and environmental factors in the etiology of autism.

[Return to Table of Contents]

References

Arvidsson, T., Danielsson, D., Forsberg, P., Gillberg, C., & Johansson, M. (1997). Autism in 3-6-year-old children in a suburb in Goteborg, Sweden. Autism, 1, 163-173.

Baird, G., Charman, T., Baron-Cohen, S., Cox, A., Swettenham, J., Wheelwright, S., Drew, A., & Kemal, L. (in press). A screening instrument at 18 months of age: A six-year follow-up study. Journal of the American Academy of Child and Adolescent Psychiatry.

Baron-Cohen, S., Cox, A., Baird, G., Swettenham, J., Nightingale, N., Morgan, K., Drew, A., & Charman, T. (1996). Psychological markers in the detection of autism in infancy in a large population. British Journal of Psychiatry, 168, 158-163.

Berry, K. E. (1997). Developmental Test of Visual-Motor Integration (fourth edition). Modern Curriculum Press.

Bohman, M., Bohman, I.L., Bjorck, P.O., & Sjoholm, E. (1983). Childhood psychosis in a northern Swedish county: Some preliminary findings from an epidemiological survey. In M.H. Schmidt & H. Remschmidt (Eds.), Epidemiological Approaches in Child Psychiatry. pp 164-173 Verlag: Stuttgart.

Brask, B.H. (1970). A prevalence investigation of childhood psychoses. In Nordic Symposium on the Care of Psychotic Children, pp 145-153. Trykningssentral: Oslo.

Bryson, S.E., Clark, B.S., & Smith, I.M. (1988). First report of a Canadian epidemiological study of autistic syndromes. Journal of Child Psychology and Psychiatry, 29, 433-445.

Bryson, S.E, & Smith, I.M.. (1998). Epidemiology of autism: prevalence, associated characteristics, and implications for research and service delivery. Mental Retardation and Developmental Disabilities Research Review, 4, 97-103.

Burd, L., Fisher, W., & Kerbeshian, J. (1987). A prevalence study of pervasive developmental disorders in North Dakota. Academy of Child and Adolescent Psychiatry, 26, 700-703.

California Department of Developmental Services. (March, 1999) Changes in the population of persons with autism and pervasive developmental disorders in California's Developmental Services System: 1987 through 1998. A Report to the Legislature, Department of Developmental Services, Sacramento.

Cialdella, P., & Mamelle, N. (1989). An epidemiological study of infantile autism in a French department (Rhone): A research note. Journal of Child Psychology and Psychiatry, 30, 165-175.

Deb, S. & Prasad, K.B. (1994). The prevalence of autistic disorder among children with learning disabilities. British Journal of Psychiatry, 165, 395-399.

Elliott, C. D. (1990). Differential Ability Scales. The Psychological Corporation: New York.

Filipek, P.A., Accardo, P.J., Baranek G.T., Cook, E.H., Dawson, G., Gordon, B., Gravel., J., Johnson, C.P., Kallen, R.J., Levy, S.E., Minshew, N.J., Prizant, B.M., Rapin, I., Rogers, S.J., Stone, W.L., Teplin, S., Tuchman, R.F., & Volkmar, F.R. (1999). The screening and diagnosis of autism spectrum disorders. Journal of Autism and Developmental Disorders, 29, 437-481.

Fombonne, E., & du Mazaubrun, C. (1992). Prevalence of infantile autism in four French regions. Social Psychiatry and Psychiatric Epidemiology, 27, 203-210.

Fombone E., du Mazaubrun, C. du, Cans, C., & Grandjean, H. (1997). Autism and associated medical disorders in a French epidemiologic survey. Journal of the American Academy of Child Adolescent Psychiatry, 36, 1561-1569.

Fombonne, E. (1998). Inflammatory bowel disease and autism. Lancet, 351, 955.

Fombonne E. (1999). The epidemiology of autism: A review. Psychological Medicine, 29, 769-786.

Gillberg, C. (1984). Infantile autism and other childhood psychoses in a Swedish urban region. Epidemiologic aspects. Journal of Child Psychology and Psychiatry, 25, 35-43.

Gillberg, C., Gillberg, I.C., & Ahlsen, G. (1994). Autistic behaviour and attention deficits in tuberous sclerosis: A population-based study. Developmental Medicine and Child Neurology, 36, 50-56.

Gillberg, C., Steffenburg, S., & Schaumann, H. (1991). Is autism more common now than ten years ago? British Journal of Psychiatry, 158, 403-409.

Gillberg, C., & Wing, L., (1999). Autism: Not an extremely rare disorder. Acta Psychiatrica Scandinavica, 99, 399-406.

Honda, H., Shimizu, Y., Misumi, K., Niimi, M., & Ohashi, Y. (1996). Cumulative incidence and prevalence of childhood autism in children in Japan. British Journal of Psychiatry, 169, 228-235.

Hoshino, Y., Yashima, Y., Ishige, K., Tachibanam, R., Watanabe, M., Kancki, M., Kumashiro, H., Ueno, B., Takahashi, E., & Furukawa, H. (1982). The epidemiological study of autism in FukushimaKen. Folia Psychiatrica et Neurologica Japonica, 36, 115-124.

Ishii, T. & Takahashi, I. (1983). The epidemiology of autistic children in Toyota, Japan: Prevalence. Japanese Journal of Child and Adolescent Psychiatry, 24, 311-321.

Kadesjo, B., Gollberg, C., & Hagberg, B. (1999). Autism and Asperger Syndrome in seven-year-old children: A total population study. Journal of Autism and Developmental Disorders, 29, 327-331.

Kanner, L., & Eisenberg, L. (1956). Early infantile autism 1943-1955. American Journal of Orthopsychiatry, 26, 55-65.

International Statistical Classification of Diseases and Related Health Problems (ICD), Tenth Revision. (1992). Geneva: World Health Organization.

Lord, C. (1998). The Autism Diagnostic Observation Schedule-Generic (ADOS-G). Paper presented at the NIH State of the Science in Autism: Screening and Diagnosis Working Conference, Bethesda, MD.

Lord, C., & Risi, A. (1998). Frameworks and methods in diagnosing autism spectrum disorders. Mental Retardation and Developmental Disabilities Research Reviews, 4, 90-96.

Lord, C., Rutter, M., Goode, A., Heemsbergen, J., Jordan, H., Mawhood, L., & Schopler, E. (1989). Autism Disagnositc Observation Schedule: A standardized observation of communicative and social behavior. Journal of Autism and Developmental Disorders, 19, 185-212.

Matuishi, T., Shiotsuki, Y., Yoshimura, K., Shoji, H., Imuta, F., Yamashita, F. (1987). High prevalence of infantile autism in Kurume City, Japan. Journal of Child Neurology, 2, 268-271.

McCarthy, P., Fitzgerald, M. & Smith, M.A. (1984). Prevalence of childhood autism in Ireland. Irish Medical Journal, 77, 129-130.

Ritvo, E.R., Freeman, B.J., Pingree, C., Mason-Brothers, A., Jorde, L., Jenson, W.R., McMahon, Petersen, P.B., Mo, A. & Ritvo, A. (1989). The UCLA-University of Utah epidemiologic survey of autism: prevalence. American Journal of Psychiatry, 146, 194-199.

Sparrow, S. S., Balla, D. A., & Cicchetti, D. V. (1984). Vineland Adaptive Behavior Scales (survey edition). American Guidance Service: Circle Pines, MN.

Spiker, D. (1999). The role of genetics in autism. Infants and Young Children, 12, 55-63.

Sponheim, E., & Skjeldal, O. (1998). Autism and related disorders: Epidemiological findings in a Norwegian study using ICD-10 diagnostic criteria. Journal of Autism and Developmental Disorders, 28, 217-227.

Steinhausen, H., Gobel, D., Breinlinger, M., & Wohlleben, B. (1986). A community survey of infantile autism. Journal of the American Academy of Child Psychiatry, 25, 186-189.

Sugiyama, T., & Tokuichiro, A. (1989). The prevalence of autism in Nagoya, Japan: A total population study. Journal of Autism and Developmental Disorders, 19, 87-96.

Szatmari, P., Jones, M.B., Zwaigenbaum, L., & MacLean, J.E. (1998). Genetics of autism: Overview and new directions. Journal of Autism and Developmental Disorders, 28, 351-368.

Tager-Flusberg, H., Joseph, R.M. (1999). A comparison of language abilities in high- and low-functioning children with autism. Paper presented at the Biennial Meeting of the Society for Research in Child Development. Albuquerque, New Mexico.

Tanoue, Y., Oda, S., Asano, F., & Kawashima, K. (1988). Epidemiology of infantile autism in southern Ibaraki, Japan: differences in prevalence in birth cohorts. Journal of Autism and Developmental Disorders, 18, 155-166.

Treffert, D.A. (1970). Epidemiology of infantile autism. Archives of General Psychiatry, 22, 431-438.

Webb, E.V.J., Lobo, S., Hervas, A., Scourfield, J., & Fraser, W.I. (1997). The changing prevalence of autistic disorder in a Welsh health district. Developmental Medicine and Child Neurology, 39, 150-152.

Wing, L. (1993). The definition and prevalence of autism: A review. European Child Adolescent Psychiatry, 2, 61-74.

Wing, L., & Gould, J. (1979). Severe impairments of social interaction and associated abnormalities in children: Epidemiology and classification. Journal of Autism Developmental Disorders, 9, 11-2.

Wing, L. (1981). Sex ratios in early childhood autism and related conditions. Psychiatry Research, 5, 129-137.

[Return to Table of Contents]

Table 1. Children Identified as Possible Case-Children by Source of Diagnostic Information and Final Diagnosis.

	Source of Diagnostic Information		
Final Diagnosis	**Clinical Exam**	**Records**	**Total**
Autism Spectrum Disorder (ASD)	43	17	60
Autistic disorder	30	6	36
PDD-NOS / Asperger disorder	13	11	24
Not ASD	10	5	15
Total	53	22	75

Table 2. Prevalence of Autism Spectrum Disorder (ASD) in Brick Township, NJ, by Age in 1998.

Diagnosis	Age in 1998					
	3-5 years (N= 3,479)		6-10 years (N=5,417)		3-10 years (N=8,896)	
	No.	Rate/1,000 (95% CI)	No.	Rate/1,000 (95% CI)	No.	Rate/1,000 (95%CI)
Autistic disorder	19	5.5 (3.3 - 8.5)	17	3.1 (1.8 - 5.0)	36	4.0 (2.8 -5.6)
PDD-NOS/Asperger's disorder	8	2.3 (1.0-4.5)	16	3.0 (1.7-4.8)	24	2.7 (1.7-4.0)
Total ASD	27	7.8 (5.1-11.3)	33	6.1 (4.2–8.5)	60	6.7 (5.1 - 8.7)

PDD-NOS = pervasive developmental disorder–not otherwise specified

Table 3. Prevalence of Autism Spectrum Disorder (ASD) in Brick Township, NJ, by Sex

Diagnosis	Sex Male (N= 4,532) No.	Rate/1,000 (95% CI)	Female (N=4,364) No.	Rate/1,000 (95% CI)	Male/Female Prevalence Ratio
Autistic disorder	25	5.5 (3.6-8.1)	11	2.5 (1.3 - 4.5)	2.2 (1.1 - 4.4)
PDD-NOS/ Asperger's disorder	19	4.2 (2.5-6.5)	5	1.1 (0.4-2.7)	3.7 (1.4-9.8)
Total ASD	44	9.7 (7.1- 13.0)	16	3.7 (2.1 - 5.9)	2.7 (1.5-4.7)

PDD-NOS - pervasive developmental disorder– not otherwise specified

Table 4. Distribution of Intellectual Quotient (IQ) Score* by Autism Spectrum Disorder Diagnosis (ASD).

	IQ Score				
Diagnosis	<50	50 - 70	71 - 85	>85	Not testable **
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Autistic disorder (N=30)	6 (20)	9 (30)	6 (20)	5 (17)	4 (13)
PDD-NOS/ Asperger's disorder (N=15)	0 (0)	6 (40)	4 (27)	5 (33)	0 (0)
All ASD (N=45)	6 (13)	15 (33)	10 (22)	10 (22)	4 (9)

* IQ information was not available for 15 children.

** Four children could not complete testing with the DAS because of limited language ability and/or cooperation. These children were considered to have moderate to severe mental retardation with Vineland composite and communication standard score of less than 50.

PDD-NOS = Pervasive developmental disorder–not otherwise specified

Table 5. Number of Children with Autism Spectrum Disorder (ASD) who have Siblings with a Developmental Disability, by Diagnosis .

Diagnosis	**Number of case children with diagnosed siblings**
ASD	7**
Non-ASD developmental disability*	6
Attention deficit hyperactivity disorder	3
Speech/language/auditory disorders	2
Down syndrome	1
Cerebral palsy	1

** Three sibling pairs (including 6 case-children) from three families were included in the prevalence study.

* Numbers total 7 because one child had two siblings with different DD's.

Table 6. Summary of Epidemiologic Studies Examining the Prevalence of Autism, by Characteristics of the Studies

Author	Diagnostic Criteria	Rate/1,000 (95% CI)*	No. Children with Autistic Disorder	No. Children in Population	Male/Female Ratio	IQ ≤70 %
Lotter, 1966	Kanner	0.45 (0.31-0.62)	35	78,000	2.6	84
Brask, 1972	Kanner	0.43 (0.26-0.66)	20	46,500	1.5	-
Wing & Gould, 1979	Kanner	0.49 (0.29-0.78)	17	34,700	16.0	70
Hoshino et al., 1982	Kanner	0.23 (0.19-0.27)	142	609,848	9.9	-
Ishii & Takahashii, 1983	DSM III	1.60 (1.21-2.08)	56	35,000	6.0	-
Bohman et al., 1983	Rutter	0.56 (0.40-0.77)	39	69,000	1.6	80
Gillberg, 1984	DSM-III	0.40 (0.30-0.52)	51	128,600	1.8	78
McCarthy et al., 1984	DSM III	0.43 (0.29-0.62)	28	65,000	1.3	-

Steinhausen et al., 1986	Rutter	0.19 (0.14-0.24)	52	279,616	2.3	-
Matsuishi et al., 1987	DSM-III	1.55 (1.16-2.04)	51	32,834	4.0	nr
Burd et al., 1987	DSM-III	0.33 (0.25-0.42)	59	180,986	2.7	nr
Bryson et al., 1988	DSM-III-R	1.01 (0.62-1.54)	21	20,800	2.5	76
Tanoue et al., 1988	DSM-III	1.38 (1.16-1.64)	132	95,394	4.1	nr
Ritvo et al., 1989	DSM-III	0.25 (0.21-0.28)	241	769,620	3.7	66
Cialdella & Mammelle, 1989	Rutter	0.45 (0.34-0.56) -	61	135,180	2.0	nr
Sugiyama & Abe, 1989	DSM-III	1.30 (0.74-1.95)	16	12,263	nr	nr
Gillberg et al., 1991	DSM-III-R	0.95 (0.74-1.19)	74	78,100	2.9	82
Fombonne & du Mazaubrun, 1992	DSM-III	0.49 (0.41-0.57)	154	274,816	2.1	87
Webb et al., 1997	DSM-III-R	0.72 (0.54-0.95)	53	73,301	6.6	-

Baron-Cohen et al., 1996	ICD-10	0.63 (0.30-1.15)	10	16,000	nr	-
Honda et al., 1996	ICD-10	2.11 (1.26-3.35)	18	8,537	2.6	50
Fombonne et al., 1997	ICD-10	0.54 (0.46-0.62)	174	325,347	1.8	88
Arvidsson et al., 1997	ICD-10	3.10 (1.16-6.84)	6	1,941	5.0	100
Sponheim & Skejeldal, 1998	ICD-10	0.38 (0.25-0.56)	25	65,688	1.9	64
Kadesjo, Gillberg & Hagberg, 1999	ICD-10	6.00 (1.90-14.10)	5	826	**	60
Baird, et al., in press	ICD-10	3.08 (2.29- 4.06)	50	16,235	15.7	40

* Confidence intervals computed by authors.

** All 5 children were boys

Appendix

Autistic Disorder 299.00

A. A total of six (or more) items from (1), (2), and (3), with at least two from (1), and one each from (2) and (3):

(1) Qualitative impairment in social interaction, as manifested by at least two of the following:
  (a) marked impairment in the use of multiple nonverbal behaviors such as eye- to-eye gaze, facial expression, body postures, and gestures to regulate social interaction
  (b) failure to develop peer relationships appropriate to developmental level
  (c) a lack of spontaneous seeking to share enjoyment, interest, or achievements with other people (e.g., by a lack of showing, bringing or pointing out object of interest)
  (d) lack of social or emotional reciprocity

(2) qualitative impairments in communication as manifested by at least one of the following:
  (a) delay in, or total lack of , the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)
  (b) in individuals with adequate speech, marked impairment in the ability to initiate of sustain a conversation with others
  (c) stereotyped and repetitive use of language or idiosyncratic language
  (d) lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level

(3) restricted repetitive and stereotyped patterns of behavior, interests, and activities, as manifested by at least one of the following:
  (e) encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
  (f) apparently inflexible adherence to specific, nonfunctional routines or rituals
  (g) stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole-body movements)
  (h) persistent preoccupation with parts of objects

B. Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years: (1) social interaction, (2) language as used in social communication, or (3) symbolic or imaginative play.

C. The disturbance is not better accounted for by Rett's Disorder or Childhood

Disintegrative Disorder.

Asperger's Disorder 299.80

A. Qualitative impairment in social interaction, as manifest by at least two of the following:
    (1) marked impairment in the use of multiple nonverbal behaviors such as eye- to-eye gaze, facial expression, body postures, and gestures to regulate social interaction
    (2) failure to develop peer relationships appropriate to developmental level
    (3) a lack of spontaneous seeking to share enjoyment, interest, or achievements with other people (e.g., by a lack of showing, bringing or pointing out object of interest)
    (4) lack of social or emotional reciprocity

B. Restricted repetitive and stereotyped patterns of behavior, interests, and activities, as manifested by at least one of the following:
    (1) encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
    (2) apparently inflexible adherence to specific, nonfunctional routines or rituals
    (3) stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole-body movements)
    4) persistent preoccupation with parts of objects

C. The disturbance causes clinically significant impairment in social, occupational, or other important areas of functioning.

D. There is no clinically significant general delay in language (e.g., single words used by age 2 years, communicative phrases used by age 3 years).

E. There is no clinically significant delay in cognitive development or in the development of age-appropriate self-help skills, adaptive behavior (other than in social interaction), and curiosity about the environment in childhood.

F. Criteria are not met for another specific Pervasive Developmental Disorder or Schizophrenia.

Pervasive Developmental Disorder Not otherwise Specified - 299.80
(Including Atypical Autism)

This category should be used when there is a severe and pervasive impairment in the development of reciprocal social interaction or verbal and nonverbal communication skills, or when stereotyped behavior, interest, and activities are present, but the criteria are not met for a specific Pervasive Developmental Disorder, Schizophrenia, Schizotypal Personality Disorder, or Avoidant Personality Disorder. For example, this category includes "atypical autism"–presentations that do not meet the criteria for Autistic Disorder because of late age at onset, atypical symptomatology or subthreshold symptomatology, or all of these.

Brick Township Investigation Report Release
Schedule of Events
April 18, 2000

Monday April 17th	Travel to New Jersey	
Tuesday April 18th		
8:30 – 10:00	Meet with Gallaghers & Eric London	Gallager's Home 508 Carroll Fox Rd Brick, NJ 732/295-5739
10:30 – 11:30	Meet with town officials	Brick Town Hall 401 Chambers Bridge Brick, NJ 732/262-1050
	LUNCH	
2:00 – 4:00	Media availability session	Brick Town Hall
	DINNER	
6:00 – 8:00	Public availability session	Brick Town Hall
Wednesday April 19th	Return to Atlanta	

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

ATSDR

Fact Sheet

CDC/ATSDR Involvement in the Brick Township Autism Investigation

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Embargoed until 4 p.m. ET	CDC, Media Relations **(404) 639-3286**
Tuesday, April 18, 2000	ATSDR Office of Policy and External Affairs **(404) 639-0501**

- In late 1997, a citizen's group in Brick Township, New Jersey (NJ), provided results of a survey to the New Jersey Department of Health and Senior Services that suggested that the number of Brick Township children with autism could be potentially several times higher than expected based on available prevalence rates for the disorder.
- In early 1998, the Centers for Disease Control and Prevention (CDC) and the Agency for Toxic Substances and Disease Registry (ATSDR) were contacted by the N.J. Department of Health and Senior Services, U.S. Senator Robert Torricelli, and U.S. Representative Christopher Smith requesting the possibility of federal assistance in addressing the concerns of the citizens of Brick Township.
- CDC assistance was requested because of the complexity of investigating a behavioral disorder such as autism and the fact that CDC was developing epidemiological methods that address the unique challenges of autism. ATSDR's expertise was requested because community members felt environmental factors might be involved.
- ATSDR conducted a scientific literature review to determine what is known about associations between chemical contaminants and autism. ATSDR investigators also assessed whether any environmental pathways for human exposure exist in Brick Township. ATSDR also developed a plan for community involvement and health education activities.
- CDC investigators with expertise in population-based studies of autism conducted the prevalence investigation. Their report was provided to the parents of the children who participated in the study in Brick Township and the general public through the CDC's web site at: http://www.cdc.gov/nceh/programs/cddh.

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

Fact Sheet

CDC Examines Autism Among Children

Embargoed until 4 p.m. ET Tuesday, April 18, 2000   CDC, Media Relations **(404) 639-3286**

- It is not known how many children in the United States currently have autism or a related disorder. Studies done in Europe and Asia indicate as many as 2 out of every 1,000 children have some type of autism.

- A recent investigation by CDC in Brick Township, New Jersey, found a prevalence rate for the autism of 4.0 per 1,000 children and a rate of 6.7 per 1,000 children for the more broadly defined category of autistic spectrum disorders. Although the rates obtained in Brick are high compared to other published reports, it is important to keep in mind that there are no current rates for autism from the United States.

  Furthermore, investigators in other countries who used intense case finding methods in small communities are finding rates of autism in the range of those found in Brick Township. The interpretation of the results from the Brick prevalence investigation will not be fully understood until additional prevalence rates have been obtained from other communities and compared to those in Brick Township.

- CDC runs the Metropolitan Atlanta Developmental Disabilities Surveillance Program (MADDSP), one of the few programs in the world that conducts active and ongoing monitoring of the number of children with developmental disabilities in the multiracial Atlanta area. CDC added autism to the program in 1998 and anticipates having prevalence rates for autism in the fall of 2000.

- Autism is a spectrum of disorders that are complex and lifelong. Individuals with autism have problems with social interaction, communication difficulties, and restrictive or repetitive interests/behaviors. Autism Spectrum Disorders (ASD) includes autistic disorder, pervasive developmental disorder - not otherwise specified (also known as atypical autism), and Asperger's disorder as defined by the American Psychiatric Association's Diagnostic and Statistical Manual - Fourth Edition (DSM-IV).

- Children with autism require long-term care and services. Special education costs for a child with autism are more than $8,000 per year, with some specially structured programs costing about $30,000, and care in a residential school costing $80,000 -

$100,000 per year.

- Little is known about causes of autism, although genetic and early prenatal exposures have been suggested. There is no cure for autism. However, early and intensive education can help children develop skills and reach their potential. Although available medicines cannot cure autism, some may relieve symptoms associated with the disorders.

Other Related CDC Activities

- CDC funds Marshall University Autism Training Center, West Virginia, to develop and implement a program to prevent secondary conditions among children with autism and their families. Marshall University is also developing a prevalence system for autism in six counties of West Virginia.

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

Fact Sheet

Investigation of the Prevalence of Autism in Brick Township
A Community Report

Embargoed until 4 p.m. ET Tuesday, April 18, 2000 CDC, Media Relations **(404) 639-3286**

- At the request of the New Jersey Department of Health and Senior Services and congressional district representatives, the Centers for Disease Control and Prevention (CDC) and the Agency for Toxic Substance and Disease Registry (ATSDR) investigated if the rates of autism among children in Brick Township, New Jersey were higher than expected. Published prevalence rates were examined and researchers looked into whether there were possible links to environmental exposures.

- Autism is a spectrum of disorders that are complex and lifelong. Individuals with autism have problems with social interactions and communication skills as well as a tendency towards restrictive or repetitive interests and behaviors. Autism spectrum disorders (ASD) is a term used to describe the continuum of functioning among persons with autism. ASD includes autistic disorder, pervasive developmental disorder - not otherwise specified, and Asperger's disorder as defined by the American Psychiatric Association's Diagnostic and Statistical Manual - Fourth Edition (DSM-IV).

- CDC's expertise was called upon because of the complexity of investigating a behavioral disorder such as autism and the fact that CDC was developing epidemiologic methods that address the unique challenges of autism.

- The prevalence investigation identified children with possible autism whose parents were residents of Brick Township during 1998. The autism diagnosis was verified through a clinical assessment.

- The rate of autism among children in Brick Township was 4.0 per 1,000 children aged 3 through 10 years. The prevalence of the more broadly defined autism spectrum disorder was 6.7 per 1,000 children. These prevalence rates are higher than rates reported in other currently published studies from other countries.

- Whether the Brick Township rate is unusual relative to other U.S. communities is uncertain. No current data on the prevalence of autism in the U.S. is available.

- A few very recent studies in other countries have found high rates. Service provider data in the U.S., e.g., special education data, show increasing numbers of children with autism receiving specialized services.

- There is ongoing scientific discussion about whether higher rates of autism worldwide reflect a true increase over time, a greater awareness of these disorders, improved case finding techniques, broader diagnostic criteria, or a combination of all these factors.

- Other results from the Brick Township investigation:
    - Sixty of the 75 potential case children met the criteria (DSM-IV) for an ASD.
    - Thirty-six of the children met the criteria for autistic disorder.
    - There were twice as many boys than girls with autistic disorder.
    - Sixty-three percent of the children had mental retardation.
    - Seven children had a brother or sister who also had an ASD.

- Because of the lack of data on autism in the U.S., monitoring the prevalence of these disorders in several communities across the country would be helpful to identify the magnitude of this health problem and how it varies in different population subgroups. In addition, we need to do large-scale epidemiologic studies to begin to understand the cause of this important health problem.

ATSDR

Fact Sheet

Results of Brick Township Investigation of Environmental Pathways - A Public Health Assessment

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Embargoed until 4 p.m. ET Tuesday, April 18, 2000 ATSDR Office of Policy and External Affairs, at (404) 639-0501

At the request of the New Jersey Department of Health and Senior Services, local parents, members of Congress, the Centers for Disease Control and Prevention (CDC), and the Agency for Toxic Substances and Disease Registry (ATSDR) agreed to investigate the prevalence of autism cases in Brick Township and to also determine if there was an environmental explanation.

ATSDR, a federal public health agency that deals with hazardous waste issues related to human health, conducted the investigation which looked for environmental explanations. ATSDR reviewed environmental sampling data from the Environmental Protection Agency (EPA), the New Jersey Department of Environmental Protection (NJDEP), the Ocean County Health Department (OCHD), and the Brick Township Municipal Utilities Authority to assess the possibilities of past and current exposure to hazardous substances.

ATSDR has prepared this public health assessment to address hazardous chemicals in the environment for three areas: the municipal drinking water supply, swimming in the Metedeconk River, and the Brick Township landfill. After a thorough examination of data for each of these areas, ATSDR researchers concluded that, while chemicals may have been found, neither children nor pregnant women were exposed to levels which would be likely to cause adverse health effects.

Public Health Conclusions

- ATSDR looked at information for the Brick Township municipal drinking water system from 1987 to 1995 and found that, during this period, the water at various times contained several substances, which included tetracholoroethylene (PCE), trichloroethylene (TCE), and trihalomethanes (THMs).

(732) 477-4513

If you have questions about the public health assessment or would like to obtain a copy, contact Robert Knowles, ATSDR environmental scientist, toll free at 1-888-42-ATSDR (1-888-422-8737).

Additional Resources:

CDC's National Center for Environmental Health has prepared a report of its findings for the prevalence of autism spectrum disorders in Brick Township. To obtain a copy of that report, go to the web site at http://www.cdc.gov. A copy can also be obtained at the Brick Library or by calling the Developmental Disabilities Branch at 1-770-488-7360.

ATSDR reviewed scientific literature dealing with hazardous substance exposure and autism. The results of the literature review were published in a health consultation released for public comment by ATSDR in December 1998. To obtain a copy of that health consultation, contact ATSDR's Information Center, toll free, at 1-888-42-ATSDR (1-888-422-8737).

Additional information on the health affects of exposure to Tetrachloroethylene and Trichloroethylene are available at ATSDR's web site. The address is: http://www.atsdr.cdc.gov. Click on ToxFAQs™ and follow the alphabetical listings of substances. For information on Trihalomethanes and other disinfection by-products, you can go to the EPA Envirofacts home page at http://www.cdc.gov/enviro.

Mr. BURTON. Dr. Taylor, you have shown the measles virus in the intestine, and you have in your laboratory—or "laboratory," as they call it in your country—you have gone through and checked those samples that were sent to you by Dr. Wakefield that show that there definitely was measles in the gut of these children who became autistic. I think Dr. Singh verified the same thing.

Did you check any of that, Dr. Taylor, why there was measles in the guts of those children? Did you take a look at any of that?

Dr. TAYLOR. I am sorry, I have not had a chance to look at this paper. It is interesting information. However, in terms of Mr. Wakefield's history, in all of his initial results, he has found the cure for, first of all, Crohn's disease, and he has found the cure for——

Mr. BURTON. Let me just ask you this—I do not want to go into those other things—Dr. Wakefield showed us on his slides that there was measles in the guts of these children who were vaccinated with the MMR shot. Professor O'Leary verified it in a separate laboratory——

Dr. TAYLOR. Not in a separate laboratory; that was the same laboratory. That, I think, is the critical point.

Mr. BURTON. Well, it was——

Dr. TAYLOR. This information does have to be verified by an independent laboratory.

Mr. BURTON [continuing]. It was sent to him—and Dr. Singh, I think, verified it as well. You have not, though, looked into the problem with the measles in the gut of these children, though?

Dr. TAYLOR. I do not know quite what you mean. That is not my area.

Mr. BURTON. You have not checked into that; OK.

Professor O'Leary, did you want to say something?

Dr. O'LEARY. Sir, can I make a comment, please? What I presented is evidence, direct evidence, cell-based and tube-based. It was done at a separate laboratory from Dr. Wakefield's.

If Professor Taylor has a beef with me, he should say that. My work is completely independent. I stand over it. I have come here to tell the truth. There is nothing for me to be gained in not telling the truth.

Mr. BURTON. Dr. Singh, you had some more comments, and I want to yield the balance of my time to you to respond.

Mr. SINGH. Yes, just a couple of things. Basically, I want to raise the issue that when we think about epidemiological studies, what are these individuals really looking at. All they do is they take numbers from previous, old records of what-have-you. They do not even pay any attention to the fact that old-time vaccines were made based on old immunology. Today, immunology is so different; it is almost a difference of day and night. So we need to take into account that new research should really be evaluated by so-called expert epidemiologists.

The second thing——

Mr. BURTON. Well, let me just say one more thing. I want to ask Dr. Boyle one last question, and that is do you believe anybody who is getting funds from Merck or any of the other pharmaceutical companies should be on advisory panels that are making judgments about pharmaceuticals coming from those companies, or do you believe that that is a conflict of interest?

Ms. BOYLE. I think that is a difficult question to answer.

Mr. BURTON. Wait a minute. Let me get this straight. You think it is a difficult question to answer. If somebody is getting funding of some type from a pharmaceutical company, for them to sit on an advisory panel that is approving or giving their approval to a new drug that is coming on the market, you do not see that as a conflict?

Dr. SCHWARTZ. Mr. Chairman, I am Dr. Schwartz. I am a colleague of Dr. Boyle and am the acting director of the Epidemiology and Surveillance Division in the National Immunization Program, and we appreciate your indulgence in allowing me to testify and to help with answering questions about immunization.

The Advisory Committee on Immunization Practices is a chartered advisory committee under the FACA regulations. There are very strict guidelines regarding the participation in votes of members who may have conflicts of interest that will help assure that those potential conflicts of interest, those potential financial conflicts, do not affect the votes and the decisions of the advisory committee.

The reason why individuals who may potentially have conflicts are included in the committee is to assure that we get the best expert advice possible so that we can make the best vaccine recommendations possible, and frequently, the best experts are those who may have done research or may have provided information to some of the vaccine manufacturers—but their role in the committee and in the voting process is very strictly defined.

It is also important to point out that recommendations for vaccination are made independently by the American Academy of Pediatrics and the American Academy of Family Physicians, and those recommendations are virtually always in harmony with the recommendations from the Advisory Committee on Immunization Practices.

Mr. BURTON. Well, I am going to go ahead—my time is expired, but I am going to come back to you on that. I will take another round on that.

Mr. Waxman.

Mr. WAXMAN. I want to say to the parents in the audience and to others, family members, who are here that I do not want you to think that I am in any way trying to minimize what you have gone through or to in any way challenge the depth and sincerity of your feelings. I think that is a separate question from the scientific question of whether there is a causal link. And because it is so important, it is essential that through sound science, we determine this fact—not through emotionalism and not through sensationalism.

I did not come here to say one side is right or one side is wrong, but I want us to have the best scientific information we can have.

Now, Dr. Offit's integrity has been challenged, presumably because he has a point of view that does not quite fit with the chairman's point of view. Dr. Schwartz started to indicate why he thought your situation, even though you have a relationship with Merck, did not put you in a conflict.

Let me ask you directly, Dr. Offit, do you have a conflict of interest, and if "No," why not?

Dr. OFFIT. No, I have no conflict of interest. What I have is an apparent conflict of interest, and that is why I disclosed that at the beginning of every ACIP meeting, and that is why I disclosed it in my written report.

If I could just explain this a little bit, I have been doing research for 20 years on rotaviruses. What I have done in my laboratories is try, with my colleagues, to understand what the genes are that cause diarrhea and what the genes are that help the body fight infection. That led to a patent on a vaccine for rotavirus. Rotaviruses kill 13 children a day in this world, and rotaviruses cause 1 out of every 75 children born in this country to be hospitalized. It is a serious, and in developing countries often a deadly, infection.

It would be an advance if we could prevent that disease. Merck and Company has made a commitment to developing that vaccine, and hopefully, if we can develop a safe and effective vaccine, we can prevent a lot of disease and death.

Mr. WAXMAN. I think that everyone here should agree that we want a safe vaccine, or a vaccine that is as safe as possible. Merck did not hire you to come up with a particular position, did they? Did they tell you they wanted your research to have a certain outcome?

Dr. OFFIT. No. This work was all done—frankly, it was funded by the National Institutes of Health, and it was funded by research that we did as a basic—I am an immunologist—that is my expertise.

Mr. WAXMAN. There is an organization—and I am going to put this in the record—called the Autism Autoimmunity Project. I have a letter from its president urging people to give money to it, because this project is going to fund research that is going to show the connection between vaccines and autism and other diseases. And they proudly say they fund Dr. Wakefield and Dr. Singh. Is that true?

Mr. SINGH. Yes.

Mr. WAXMAN. Is that true, Dr. Singh?

Mr. SINGH. Yes. I just received some money from that foundation, oh, about 2 months ago. My research has been going on on this issue for the last 15 years.

Mr. WAXMAN. Yes—and I am not saying there is anything wrong with it——

Mr. SINGH. I just wanted to make a point on that.

Mr. WAXMAN [continuing]. Although this organization seems to have a particular point of view. How would you think they would feel if your research came up with a different conclusion from what they wanted to achieve in their—because they have a position——

Mr. SINGH. Mr. Waxman, I am a very honest, decent human being—unlike, perhaps, some other people that you might know of—and I can tell you that if I found a connection which was not existent or if my results did not support what this foundation wanted, I would even return the money to that foundation.

Mr. WAXMAN. Even though they want a particular point of view——

Mr. SINGH. They never asked me to do any research——

Mr. WAXMAN [continuing]. You are an independent scientist, and you have integrity.

Mr. SINGH. What I am——

Mr. WAXMAN. Just answer yes or no, because I do want to ask——

Mr. SINGH. I beg your pardon?

Mr. WAXMAN. My question to you is they have a point of view, but they fund you, you have integrity, and you are going to do your work based on science. Is that your answer?

Mr. SINGH. My answer is that I am getting funds from private sources because national agencies continue to decline my research grant proposals when I submit. Where else am I going to go to get the funding?

Mr. WAXMAN. Have you been turned down by NIH?

Mr. SINGH. I am trying to raise funding independently, on my own, not necessarily——

Mr. WAXMAN. Have you been turned down by NIH?

Mr. SINGH. Three times, I have attempted—three times, I have written grants, and NIH has not given me a single dime.

Mr. WAXMAN. I want Dr. Wakefield to be able to answer the same question very briefly.

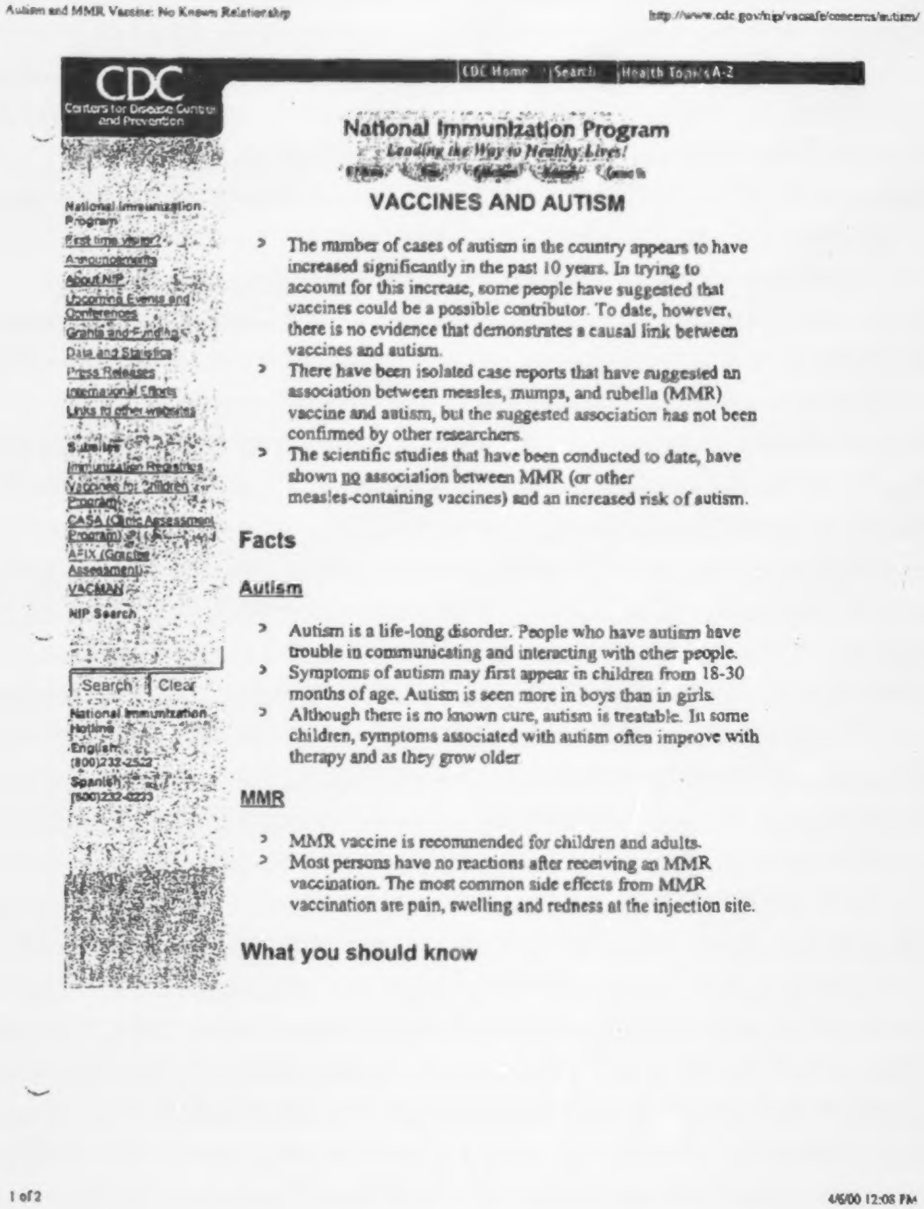
Dr. Wakefield, you acknowledge you have received money. Do you feel that that in any way raises expectations that your research come out with a result that this organization wants?

Dr. WAKEFIELD. We are funded to test hypotheses, and we present the data whether the hypothesis is correct or not. And we have done that, we have gone on record as doing it. We publish negative studies in association with measles and Crohn's disease. That does not mean it is not there; it means that our hypothesis was wrong in terms that we could not find it using the technology. So we have gone on record as publishing both positive and negative data.

Mr. WAXMAN. I ask unanimous consent that those documents from the Autism Autoimmunity Project be put in the record, and I would note, Mr. Chairman, that you are also associated on the board of this group.

Mr. BURTON. Without objection. That is no problem.

[The information referred to follows:]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Press Releases
International Efforts
Links to other websites
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Autism and MMR Vaccine: No Known Relationship

http://www.cdc.gov/nip/vacsafe/concerns/autism/

National Immunization Program

Leading the Way to Healthy Lives!

VACCINES AND AUTISM

- The number of cases of autism in the country appears to have increased significantly in the past 10 years. In trying to account for this increase, some people have suggested that vaccines could be a possible contributor. To date, however, there is no evidence that demonstrates a causal link between vaccines and autism.
- There have been isolated case reports that have suggested an association between measles, mumps, and rubella (MMR) vaccine and autism, but the suggested association has not been confirmed by other researchers.
- The scientific studies that have been conducted to date, have shown no association between MMR (or other measles-containing vaccines) and an increased risk of autism.

Facts

Autism

- Autism is a life-long disorder. People who have autism have trouble in communicating and interacting with other people.
- Symptoms of autism may first appear in children from 18-30 months of age. Autism is seen more in boys than in girls.
- Although there is no known cure, autism is treatable. In some children, symptoms associated with autism often improve with therapy and as they grow older.

MMR

- MMR vaccine is recommended for children and adults.
- Most persons have no reactions after receiving an MMR vaccination. The most common side effects from MMR vaccination are pain, swelling and redness at the injection site.

What you should know

1 of 2

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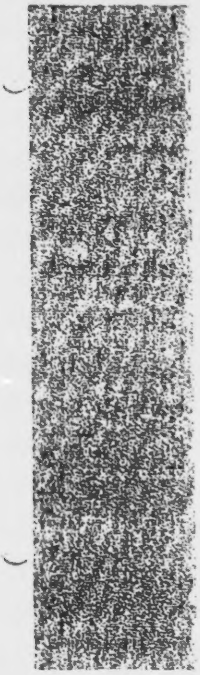

- To assure the safety of vaccines, the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the National Institutes of Health (NIH), and other Federal agencies routinely monitor and conduct research to examine any new evidence that would suggest possible problems with the safety of vaccines.
- If you wish to report a health problem that followed vaccination, you or your health care provider should call the Vaccine Adverse Event Reporting System (VAERS) at 1-800-822-7967.

For more information contact

National Immunization Program, CDC:
National Immunization Hotline: English **(800) 232-2522**,
Spanish **(800) 232-0233**

National Immunization Program web site: http://www.cdc.gov/nip

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This page last reviewed March 28, 2000

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National Immunization Program
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Announcements
About NIP
Upcoming Events and Conferences
Grants and Funding
Data and Statistics
Press Releases
International Efforts
Links to other websites
Subsites
Immunization Registries
Vaccines for Children Program
CASA (Clinic Assessment Program)
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WHAT WOULD HAPPEN IF WE STOPPED VACCINATIONS ?

Vaccines are responsible for the control of many infectious diseases that were once common in this country. However, the viruses and bacteria that cause vaccine-preventable disease and death still exist and can be passed on to people who are not protected by vaccines. Vaccine-preventable diseases have a costly impact, resulting in doctor's visits, hospitalizations, and premature deaths. Sick children can also cause parents to lose time from work.

Polio

Polio virus causes acute paralysis that can lead to permanent physical disability and even death. Before polio vaccine was available, 13,000 to 20,000 cases of paralytic polio were reported each year in the United States. These annual epidemics of polio often left thousands of victims--mostly children--in braces, crutches, wheelchairs, and iron lungs.

Development of polio vaccines and implementation of polio immunization programs have eliminated paralytic polio caused by wild polio viruses in the U.S. and the entire Western hemisphere.

In 1999, as a result of global immunization efforts to eradicate the disease, there were about 5,000 documented cases of polio in the world. In 1994, wild polio virus was imported to Canada from India, but high vaccination levels prevented it from spreading in the population.

Measles

Before measles immunization were available, nearly everyone in the U.S. got measles. There were approximately 3-4 million measles cases each year. An average of 450 measles-associated deaths were reported each year between 1953 and 1963.

In industrialized countries, up to 20% of persons with measles are hospitalized, and 7% to 9% suffer from complications such as pneumonia, diarrhea, or ear infections. Although less common, some persons with measles develop encephalitis, resulting in brain damage. It is estimated that as many as one of every 1,000 persons with measles will die.

Measles is one of the most infectious diseases in the world and is frequently imported into the U.S. In 1998, most cases were associated with international visitors or U.S. residents who were exposed to the measles virus while traveling abroad. More than 90% of people who are not immune will get measles if they are exposed to the virus.

According to the World Health Organization, nearly 900,000 deaths occurred among persons in developing countries in 1998. In populations that are not immune to measles, measles spreads rapidly. If vaccinations were stopped, 2.7 million measles deaths worldwide could be expected.

In the U.S., widespread use of measles vaccine has led to a greater than 99% reduction in measles compared with the pre-vaccine era. If we stopped immunization, measles would increase to pre-vaccine levels.

Haemophilus Influenzae Type b (Hib) Meningitis

Before Hib vaccine became available, Hib was the most common cause of bacterial meningitis in U.S. infants and children. Before the vaccine was developed, there were approximately 20,000 invasive Hib cases annually. Approximately two thirds of the 20,000 cases were meningitis, and one-third were other life-threatening invasive Hib diseases such as bacteria in the blood, pneumonia, or inflamation of the epiglotis. About one of every 200 U.S. children under 5 years of age got an invasive Hib disease. Hib meningitis killed 600 children each year, and left many survivors with deafness, seizures, or mental retardation.

Since introduction of conjugate Hib vaccine in December 1987, the incidence of Hib has declined by 98 percent. From 1994-1998, fewer than 10 fatal cases of invasive Hib disease were reported each year.

This preventable disease was a common, devastating illness as recently as 1990; now, most pediatricians just finishing training have never seen a case. If we were to stop immunization, we would likely soon return to the pre-vaccine numbers of invasive Hib disease cases and deaths.

Pertussis (Whooping Cough)

Since the early 1980s, reported pertussis cases have been increasing, with peaks every 3-4 years; however, the number of reported cases remains much lower than levels seen in the pre-vaccine era. Compared with pertussis cases in other age groups, infants who are 6 months old or younger with pertussis experience the highest rate of hospitalization, pneumonia, seizures, encephalopathy (a degenerative disease of the brain) and death. From 1990 to 1996, 57 persons died from pertussis; 49 of these were aged <6 months.

Before pertussis immunizations were available, nearly all children developed whooping cough. In the U.S., prior to pertussis immunization, between 150,000 and 260,000 cases of pertussis were reported each year, with up to 9,000 pertussis-related deaths.

Pertussis can be a severe illness, resulting in prolonged coughing spells that can last for many weeks. These spells can make it difficult for a child to eat, drink, and breathe. Because vomiting often occurs after a coughing spell, infants may lose weight and become dehydrated. In infants, it can also cause pneumonia and lead to brain damage, seizures, and mental retardation.

The newer pertussis vaccine (acellular or DTaP) that has been available for use in the United States since 1991. These vaccines are effective and associated with fewer mild and moderate adverse reactions when compared with the older (whole-cell DTP) vaccine.

During the 1970s, widespread concerns about the safety of pertussis immunization led to a rapid fall in immunization levels in the United Kingdom. More than 100,000 cases and 36 deaths due to pertussis were reported during an epidemic in the mid 1970s. In Japan, pertussis vaccination coverage fell from 80 percent in 1974 to 20 percent in 1979. An epidemic occurred in 1979, resulted in more than 13,000 cases and 41 deaths.

Pertussis cases occur throughout the world. If we stopped pertussis immunizations in the U.S., we would experience a massive resurgence of pertussis disease. A very recent study found that, in eight countries where immunization coverage was reduced, incidence rates of pertussis surged to 10 to 100 times the rates in countries where vaccination rates were sustained.

Rubella (German Measles)

While rubella is usually mild in children and adults, up to 90 percent of infants born to mothers infected with rubella during the first trimester of pregnancy will develop congenital rubella syndrome (CRS), resulting in heart defects, cataracts, mental retardation, and deafness.

In 1964-1965, before rubella immunization was used routinely in the U.S., there was an epidemic of rubella that resulted in an estimated 20,000 infants born with CRS, with 2,100 neonatal deaths and 11,250 miscarriages. Of the 20,000 infants born with CRS, 11,600 were deaf, 3,580 were blind, and 1,800 were mentally retarded.

Many developing countries do not include rubella in the childhood immunization schedule. Since 1996, greater than 50% of the reported rubella cases have been among adults. Sites of exposure for several outbreaks have included workplaces and communities. In 1998, 12 outbreaks of rubella occurred resulting in 19 pregnant women contracting rubella.

If we stopped rubella immunization, immunity to rubella would decline and rubella would once again return, resulting in pregnant women becoming infected with rubella and then giving birth to infants with CRS. Incidence of CRS declined dramatically with widespread use of rubella vaccine.

Varicella (Chickenpox)

Chickenpox is always present in the community and is highly contagious. Prior to the licensing of chicken pox vaccine in 1995, almost all persons in the U.S. had suffered from chickenpox by adulthood. Chicken pox was responsible for an estimated 4 million cases, 11,000 hospitalizations, and 100 deaths each year.

Chicken pox is usually mild, but may be severe in some infants, adolescents, and adults. Some people who get chicken pox have also suffered from complications such as secondary bacterial infections, loss of fluids (dehydration), pneumonia, and central nervous system involvement. In addition, only persons who have had chicken pox in the past can get shingles, a painful inflamation of the nerves. There are about 300,000 cases of shingles that occur each year when inactivated chicken pox virus is activated in people who have had chicken pox in the past.

From March 1995-August 1999, a total of 18.5 million doses of chicken pox vaccine were distributed in the United States. Vaccine coverage among children 19-35 months was 43% in 1998.

In 1990 in the U.S., the cost of caring for children who contracted chickenpox was estimated as $918 million annually. If we were to stop vaccinating for chicken pox in the U.S., this disease would quickly return to its previous high rate of infection. As a result, almost every child would miss a week of school (and the parent a week of work), and 50-100 varicella-related deaths would occur each year, most of them in previously healthy children and adults.

Hepatitis B

More than 2 billion persons worldwide have been infected with the hepatitis B virus at some time in their lives. Of these, 350 million are life-long carriers of the disease and can transmit the virus to others. One million of these people die each year from liver disease and liver cancer.

National studies have shown that five percent of Americans --1.25 million people -- have been infected with hepatitis B virus. In addition, these studies have shown that about 300,000 people have been infected with hepatitis B virus each year for the two decades prior to 1990. Currently, there are about 1.25 million people who have life-long hepatitis B virus infection. Each year about 4,000-5,000 of these people die from related liver disease resulting in over $700 million of medical and work-loss costs.

Infants and children who become infected with hepatitis B virus are at highest risk of developing lifelong infection, which often leads to death from liver disease (cirrhosis) and liver cancer. Approximately 25% of children who become infected with life-long hepatitis B virus would be expected to die of related liver disease as adults.

CDC estimates that one-third of the life-long hepatitis B virus infections in the United States resulted from infections occurring in infants and young children. About 16,000 - 20,000 hepatitis B antigen infected women give birth each year in the United States. It is estimated that 12,000 children born to hepatitis B virus infected mothers were infected each year before implementation of infant immunization programs. In addition, approximately 33,000 children (10 years of age and younger) of mothers who are not infected with hepatitis B virus were infected each year before routine childhood hepatitis B vaccination was recommended.

Diphtheria

Diphtheria is a serious disease caused by poison produced from the bacteria. It frequently causes heart and nerve problems. The death rate is 5%-10%, with higher death rates (up to 20%) in the very young and the elderly.

In the 1920's, diphtheria was a major cause of illness and death for children in the U.S. In 1921, a total of 206,000 cases and 15,520 deaths were reported. With vaccine development in 1923, new cases of diphtheria began to fall in the U.S., until in 1998 only one case was reported.

Although diphtheria is rare in the U.S., it appears that the bacteria continues to get passed among people. In 1996, 10 isolates of the bacteria were obtained from persons in an American Indian community in South Dakota, none of whom had classic diphtheria disease. There has been one death reported in 1999 from clinical diphtheria caused by a related bacteria.

There are high rates of susceptibility among adults. Screening tests conducted since 1977 have shown that 41%-84% of adults 60 and over lack protective levels of circulating antitoxin against diphtheria.

Although diphtheria is rare in the U.S., it is still a threat. Diphtheria is common in other parts of the world and with the increase in international travel, diphtheria and other infectious diseases are only a plane ride away. If we stopped immunization, the U.S. might experience a situation similar to the Newly Independent States of the former Soviet Union. With the breakdown of the public health services in this area, diphtheria epidemics began in 1990, fueled primarily by persons who were not properly vaccinated. From 1990-1998, more than 150,000 cases and 5,000 deaths were reported.

Tetanus (Lock Jaw)

Tetanus is a severe, often fatal disease. The bacteria that cause tetanus are widely distributed in soil and street dust, are found in the waste of many animals, and are very resistant to heat and germ-killing cleaners. From 1922-1926, there were an estimated 1,314 cases of tetanus per year in the U.S. In the late 1940's, the tetanus vaccine was introduced, and tetanus became a disease that was officially counted and tracked by public health officials. In 1998, only 45 cases of tetanus were reported in the U.S.

People who get tetanus suffer from stiffness and spasms of the muscles. The larynx (throat) can close causing breathing and eating difficulties, muscles spasms can cause fractures (breaks) of the spine and long bones. Some people go into a coma, and die. Approximately 30% of reported cases end in death.

Tetanus in the U.S. is primarily a disease of adults. From 1995-1997, 35% of reported cases of tetanus occurred among persons 60 years of age or older, 60% occurred in patients greater than 60 years of age. The National Health Interview Survey found that in 1995, only 36% of adults 65 or older had received a tetanus vaccination during the preceding 10 years.

Worldwide, tetanus in newborn infants continues to be a huge problem. Every year tetanus kills 300,000 newborns and 30,000 birth mothers who were not properly vaccinated. Very recently, an increased number of tetanus cases in younger persons has been observed in the U.S. among intravenous drug users, particularly heroin users.

Tetanus is infectious, but not contagious, so unlike other vaccine-preventable diseases, immunization by members of the community will not protect others from the disease. Because tetanus bacteria is widespread in the environment, tetanus can only be prevented by immunization. If vaccination against tetanus were stopped, persons of all ages in the U.S. would be susceptible to this serious disease.

Mumps

Before the mumps vaccine was introduced, mumps was a major cause of deafness in children, occurring in approximately 1/20,000 reported cases. Mumps is usually a mild viral disease. However, rare conditions such as swelling of the brain, nerves and spinal cord can lead to serious side effects such as paralysis, seizures, and fluid in the brain.

Serious side effects of mumps are more common among adults than children. Swelling of the testes is the most common side effect in males past the age of puberty, occurring in up to 20-50% of men who contract mumps. An increase in spontaneous abortions has been found among women who develop mumps during the first trimester of pregnancy.

An estimated 212,000 cases of mumps occurred in the U.S. in 1964. After vaccine licensure in 1967, reports of mumps decreased rapidly. In 1986 and 1987, there was a resurgence of mumps with 12,848 cases reported in 1987. Since 1989, the incidence of mumps has declined, with a total of 606 cases in 1998. This recent decrease is probably due to the fact that children have received a second dose of mumps vaccine (part of the two-dose schedule for measles, mumps, rubella or MMR) and the eventual development of immunity in those who did not gain protection after the first mumps vaccination.

If we were to stop vaccination against mumps, we could expect the number of cases to climb back to pre-vaccine levels, since mumps is easily spread among unvaccinated persons.

Rotavirus

The Advisory Committee on Immunization Practices (ACIP) voted on October 22, 1999 to no longer recommend rotavirus vaccine for infants. The action is based on the results of a review of scientific data presented to the ACIP by CDC in cooperation with the FDA, NIH, and Public Health Service officials, along with Wyeth-Lederle, the manufacturer of the vaccine. Data from the review indicated a strong association between Rotashield vaccine and a rare occurrence of intussusception (bowel obstruction) among some infants during the first 1-2 weeks following vaccination.

Rotavirus and other causes of severe diarrhea remain a serious health concern for young children in the United States. In the U.S., rotavirus disease has been associated with approximately 50,000 hospitalizations and at least 20 deaths per year.

CDC has started a national education program to help parents manage severe diarrhea in children, the most serious complication of rotavirus illness. Education efforts will include outreach to parents through their health care providers and directly to parents through popular media such as parent magazines and radio public service announcements, in English and Spanish.

Parents are urged to learn steps to relieve diarrhea symptoms which may lead to severe dehydration and the need for immediate medical care. Signs of severe dehydration in children include decrease urination or wetting of diapers, crying without tears, sunken eyes, unusual drowsiness or fussiness and dry, sticky mouth.

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This page last reviewed March 28, 2000

Centers for Disease Control and Prevention
National Immunization Program

State of the Science in Autism: Report to the National Institutes of Health[1]

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[1] Authors listed served as reporters for the larger Autism Working Group. A reporter wrote the first draft of each individual section. Additional comments, and, in some cases, alternate perspectives raised by members of the Working Group or other reviewers were then incorporated into the Report. The final version of a section may not reflect the personal position of the reporter. Dr. Bristol takes responsibility for any errors in the overall paper. Direct correspondence to: Autism State-of-the-Science Report, Office of Research Reporting, NICHD, 31 Center Drive MSC 2425, Room 2A32, Bethesda, Maryland 20892-2425. Receipt of this report does not imply endorsement by the National Institutes of Health.

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245

ndings of the mechanisms underlying other developmental disorders such as fragile X syndrome and insulin-dependent diabetes mellitus led to an intensive lobby by parents of children with autism for similar advances in the study of autism. On April 10 and 11, 1995, the National Institutes of Health (NIH), in response to a Congressional request, assembled a working group of distinguished scientists at the NIH to assess the state of the science in autism, identify gaps in knowledge, and make recommendations to the NIH regarding promising areas for future research. Researchers in autism and related areas; representatives of the Autism Society of America; the Autism National Committee; and invited consultants contributed to the discussions reflected in this report.

Follow-up sessions were held at the national conferences of the Autism Society of America and the Autism National Committee. Thoughtful comments on the preliminary draft of this report were received from the April conference participants, at the follow-up parent conferences, and over a 4-month period from other professionals, parents, and self-advocates. Scientists listed as authors of the Report chaired one or more of the conference sessions. Major presentations at the conferences are summarized in the individual papers that follow the Report.

The NIH and follow-up conferences were cosponsored by the National Institute of Child Health and Human Development (NICHD), the National Institute on Deafness and Other Communication Disorders (NIDCD), the National Institute of Mental Health (NIMH), and the National Institute of Neurological Disorders and Stroke (NINDS). In keeping with the Congressional mandate, questions of interest to the NIH formed the basis for the conference and served as the framework for this report. These questions were developed by the NIH Inter-Institute Autism Conference Coordinating Committee: Duane Alexander (NICHD), conference convener; Judith Cooper (NIDCD); Felix de la Cruz (NICHD); Peter Jensen (NIMH); Marie Bristol (NICHD), Chair; Rebecca del Carmen (NIMH); Ralph Nitkin (NICHD); and Giovanna Spinella (NINDS).

DIAGNOSIS

C. Lord

Response to NIH Questions

Question 1: Is there a universally accepted definition of autism? Is there sufficient scientific evidence to support this current definition of autism spectrum disorders as separate from other developmental disorders? For the first

time, there are consistent criteria for diagnosis of autism spect rders in both DSM-IV (American Psychiatric Association, 1994) and ICD-10 (International Classification of Diseases, 10th ed., World Health Organization, 1993). The working group agreed that there is both national and international support for these newly published definitions. The precision of these definitions will continue to evolve as new research clarifies the phenotype (visible characteristics of autism). Identification of one or more biological markers for autism disorders is needed to diagnose definitely atypical cases. Strong empirical support in the DSM-IV International Field Trials and other NIH-funded research, however, indicates that *the clinical diagnosis of autism remains one of the most reliable diagnoses in psychiatric or developmental research.* Additional research is needed to establish the validity of the diagnosis in terms of criteria based on etiology, course, and response to treatment.

Definitions of Rett syndrome (RS) and childhood disintegrative disorder (CDD) also yielded clear, consistent differences from Autism (A) and from other disorders in the DSM-IV Field Trials (cf. Volkmar, following paper) and in other studies. Current definitions appear adequate for estimates of the incidence and prevalence of these disorders in the United States. The new definition of Asperger syndrome (AS) makes the distinction between A and AS clear and so provides the first opportunity to assess the incidence and prevalence of AS separate from A. A category such as Pervasive Developmental Disorder–Not Otherwise Specified (PDD-NOS) is still needed, but would be more appropriately entitled "Atypical Autism" for cases that meet some, but not all of the criteria for autism. Standard measures that yield these diagnoses across the age span from 3 years to adulthood are now available and used widely in research in North America and Europe.

Question 2: How do the characteristics of autism, Asperger syndrome, Rett syndrome, and childhood disintegrative disorder change with development? There are a number of studies in which characteristics of A, RS, and CDD are compared in different age groups of children, adolescents, and/or adults (i.e., cross-sectional studies). However, there are few studies following the same children as they age so we have little evidence of how individuals actually change across the life-span (i.e., longitudinal studies). Asperger syndrome is a term that has been used frequently with adolescents and adults rather than with young children, so we have few cross-sectional or longitudinal data on AS.

Several relatively large-scale, high quality, follow-up studies exist of psychometric (mental measurement test) data for autistic individuals. These studies have shown that the diagnosis of autism continues to apply as the children age and change, even after they have developed language. Longidata are needed for all autism spectrum disorders in order to tra duals' paths of development. Such data would enable us to define the course of the disorders, to aid in projecting clinical outcomes, and to plan for clinical intervention at various ages.

Question 3: What other disorders that occur as separate disorders in conjunction with autism (comorbid conditions) must be taken into account in the diagnosis and assessment of autism, Asperger syndrome, Rett syndrome, and childhood disintegrative disorder? Most, but not all persons with A also have some degree of mental retardation. There is now a very clear expectation in behavioral research that degree of mental retardation and severity of language deficit must be considered in designing and interpreting studies of the autism spectrum disorders. These co-occurring factors (mental retardation and degree of language deficit) have received less consideration in biomedical research. Lack of control for mental retardation and language deficits may be one reason why the replication rate of findings (i.e., multiple investigators obtaining the same findings) within biomedical research has typically been much lower than within behavioral research. The importance of diagnosis of comorbid (co-occurring) conditions such as affective disorder (e.g., depression) or obsessive-compulsive disorder, particularly in adults with autism spectrum disorders is also recognized, but standard procedures to do so are not well established. These await further research. It is particularly important to clarify the difference between true comorbidity and other ways in which symptoms from autism and different disorders may overlap.

Question 4: What additional research in autism, its related conditions, or relevant normative behaviors is needed to clarify subgroups in this heterogeneous population? Many investigators have proposed different subgroups in autism and these differ depending upon the theory that the particular research group espouses about the cause and/or central deficit in autism (e.g., language, motor problems, immune and/or serotonergic system differences). However, often the neurobiological or other feature purported to differentiate between or among subgroups is itself of questionable reliability. Studies of subgroups are important, but are premature if they are conducted using approaches that are not reliable or well established. One or more biological markers (e.g., genetic or neurochemical) is urgently needed to distinguish autism from other disorders and to distinguish subgroups within the autism spectrum disorders.

Recommendations of the Working Group on Diagnosis

1. Use of standard diagnostic procedures that operationalize (specify for research) DSM-IV/ICD-10 criteria is needed to promote communication among scientists, clinicians, and parents, and replicability acros . Diagnoses are not being made consistently in clinical or research settings.

2. Identification of individuals with AS and the investigation of external factors that validate the distinction between AS and A, and between AS and related learning disabilities is a high priority as well as investigation of the distinctions between severe autism and severe/profound mental retardation.

3. A central registry of persons with CDD is needed to enable researchers to find enough well-defined cases for the scientific study of CDD and for clinical information purposes. A standard protocol for clinical investigations of children with disintegrative disorders is also needed.

4. Longitudinal studies are crucial in order to provide data concerning differences and similarities in the individual developmental patterns (trajectories) of children with autism, particularly for the highest functioning individuals whose accomplishments may have been underestimated.

5. Establishing diagnostic criteria for very young (under age 3) children with autism is an urgent priority. The national trend away from specific diagnoses for young children in favor of generic terms such as "developmentally delayed" will result in a lack of appropriate early intervention services for children with autism. Continued development of reliable screening as well as diagnostic instruments is a critical need.

6. Studies that allow more accurate description of adults with autism, particularly those that address issues in the transition from school to work, are a high priority.

7. To be useful, studies of subgroups must be hypothesis driven (i.e., address a specific research question) and must validate subgroups using reliable, well-established measures that are not part of the diagnostic features.

8. Studies of subgroups that have been replicated across independent centers and across time, and those that address significant aspects of diagnosis such as course, response to treatment and well-defined levels of etiology (causes), pathophysiology (mechanism of structural and functional changes), and behavioral repertoire are a high priority. Studies of sex differences in autism are also clearly needed.

9. Minimum standards for comparison groups in studies of autism include comparability on mental handicap, degree of language impairment, and comorbidity (co-occurrence) of other conditions.

10. In studies of comorbidity of other disorders such as depression or obsessive-compulsive disorder, there is an urgent need to develop standard, reliable procedures for diagnosis of such disorders in individuals with autism, particularly in those with insufficient verbal skills for typical methods to be employed.

[illegible]. Research is urgently needed to assess the following interrelated q. (a) Does having autism and another disorder change the nature and particularly the response to treatment of the comorbid disorders? (b) Are persons with autism more at risk than other people for certain other disorders? (c) Are there symptoms or other disorders not currently included in the phenotype of autism that are so common in autism that they might better be considered part of autism, for example, certain movement disorders?

EPIDEMIOLOGY

E. J. Costello

Epidemiology is the branch of medical science that deals with the incidence, distribution, and control of disease in a population (Webster's). *Prevalence* refers to the rate of the disorder present in the population at a given point in time. *Incidence* refers to the number of new cases occurring in the population during a given period.

Response to NIH Questions

Question 1: What is the best, empirically substantiated estimate of the prevalence of autism spectrum disorders in children and adults in the United States, and in other countries? There are no prevalence estimates specifically for the United States, but recent studies from Canada and from Japan indicate that autism is not a rare disorder. Both studies found prevalence rates of autism greater than 10 per 10,000. However, these studies used fairly small (<100,000) samples, and the confidence limits are wide (±5 per 10,000). A rate of at least 22 per 10,000 has been estimated for the broader autism spectrum disorders. Because of similarities between the United States and Canada, the Canadian data are likely to be reasonable estimates of prevalence in the United States for most purposes. Given the available data, there is little justification for the potential costs of a national prevalence study of autism in the United States merely to estimate the prevalence of autism spectrum disorders. Money would be better spent on developmental risk-assessment or cost-benefit studies.

Question 2: What efforts are currently underway to improve estimates of prevalence of autism in children? How can these studies as planned, or with modification, answer the Congressional question regarding prevalence in the United States? There are a few studies of the prevalence of childhood disorders underway or in the planning stage. It is possible that autism could

be included in one or more of these studies. The difficulties [illegible]ing so are formidable.

There are two main approaches to obtain prevalence estimates of autism: population-based studies (finding persons with autism in the whole number of people in a country or region), or studies of treated populations (finding the number of persons with autism in the populations of treatment settings such as hospitals, clinics, special education settings). Population-based studies provide unbiased samples since everyone is potentially included, but require very large samples to identify reasonable estimates of disorders like autism (e.g., 500–1,000 households would have to be surveyed to identify 1 child with autism). It is estimated that a sample of over 100,000 children would be needed to produce reliable estimates of the prevalence of autism with greater precision than is currently available in the international epidemiologic literature. Children with autism could be counted in smaller treatment-based studies since they are usually referred for services. However, problems include the following: (a) it is difficult to be certain you have found all treatment settings; (b) not all settings will be willing to participate; and (c) well-functioning children will be underestimated since they may not be served in the special treatment settings. The NIMH has recently funded a network of university sites to conduct epidemiologic research on childhood disorders. This network of centers, called UNOC-CAP will study the *Use*, *Need*, *Outcomes*, and *Cost* of *Child* and *Adolescent* *Populations*. Both population-based and treated-sample studies will be carried out in UNOC-CAP and specific diagnostic measures will be included. These sites are already funded and procedures specific to the screening and diagnosis of complex disorders in children have been developed.

The National Health Interview Survey is too small to yield valid national estimates of autism. It also uses lay interviewers who may have difficulty in administering a respondent-based interview to identify a disorder like autism. The only U.S. study other than UNOC-CAP known to use diagnostic measures, the Project on Human Development in Chicago neighborhoods, is also too small and geographically too localized. Other ongoing national surveys are too small, do not include the relevant information, or could not be adapted easily to identify autism reliably.

Question 3: What contributions can epidemiologic research make to understanding the etiology and/or treatment of autism spectrum disorders? Knowing how many and where cases of a disorder occur in the population (*descriptive epidemiology*) is useful for assessing: (a) the number of individuals and families affected by a problem; (b) the size of the financial costs to be expected; (c) the relative cost burden to families, states, and the federal government, or to different service agencies (e.g., education, health, child welfare, juvenile justice); (d) the distribution of the cost and need for servi various geographic, ethnic, or socioeconomic groups; (e) the rise and fall in rates of the disorder over time, and, potentially, the impact of new social policies and treatments on prevalence and outcomes.

Some of the most powerful uses of epidemiology in medicine are as an analytic methodology, that is, as a way of testing hypotheses about causes of disease and the consequences of prevention or treatment strategies. The working group believes that *analytic epidemiology* can make important contributions to improving understanding of etiology, diagnosis, and treatment.

Etiology. Genetic epidemiology has already shown its importance for understanding etiology, and this importance will grow, not only as more genes are identified but as the functional roles of those genes are understood developmentally. Preventive interventions have to be based on etiologic theory; thus every intervention study is an implicit test of theory. Descriptive epidemiology can provide the basic hypotheses for interventions, as well as the methodology for testing the theory.

Diagnosis. The process of turning a taxonomy such as DSM-IV into instruments for epidemiologic studies helps to tighten the diagnostic criteria, making them more reliable for both epidemiologic and clinical purposes. The process of developing screening instruments helps to refine diagnosis by identifying the core symptoms and the range of variability of the diagnosis. Developmental epidemiology helps to track the developmental sequencing of patterns of symptoms and the impact of symptoms at one time on functioning at a later stage. Longitudinal studies also help to identify the development of compensatory strategies to cope with earlier symptoms.

Treatment. In an epidemiologic context, every treatment is an experiment, testing the validity of a causal theory. Clinical epidemiology, a highly developed aspect of research in many areas of medicine, has hardly gained a foothold yet in psychiatry or child development, but can provide a framework for comparing the cost-effectiveness of various treatment approaches, and examining the outcome of treatment trials for what they say about the causes of disorder and functional impairment.

Recommendations of the Working Group on Epidemiology

1. The Canadian data on prevalence are adequate for most U.S. uses. Rather than funding a national prevalence study of autism, autism should be included as one of the childhood disorders in the screening stage of the NIMH UNOC-CAP studies. A follow-up of all potential cases could then be done through UNOC-CAP with a more intensive evaluation, perhaps using experienced clinicians and one of the standard assessment packages currently in use in autism research. The UNOC-CAP population sample will not exceed 20,000 in all, but can establish rates of autism spectrum dis ers for the general population. It will be too small to produce reliable rates for minority populations or to allow comparisons of stable rates for different age groups. The treated samples will not exceed 4,000, and are likely to yield localized rather than national estimates. However, the data from UNOC-CAP would provide significant, cost-effective additions to current U.S. information on autism, particularly since prevalence data will be collected in the context of service use and need, cost, and treatment outcome.

2. Research should be implemented to address the following issues: (a) Variations in the longitudinal course of autism, from early childhood into adulthood: Why do some children do well and some poorly? (b) "Boundary conditions" around autism: What is the rate of strictly defined autism relative to the rates of other types of pervasive developmental disorders, and learning disabilities? (c) Patterns of autism-like deficits in families of children or adults with autism: What is the prevalence of these problems? (d) At what age do children who will develop autism become identifiable? (e) Sociodemographic correlates of autism: What are they? (f) What other disorders (e.g., seizures, depression) may occur during different developmental stages and in which subgroups in autism? (g) Costs associated with the appropriate treatment of children with autism: What are the costs associated with different types of lifetime support of persons with autism and their families? The working group believes that these issues can best be addressed in developmentally focused, longitudinal epidemiologic studies that follow families over time. Such studies need to include not only the child but also the family.

3. There was support in the working group for a national autism registry. Registries have proved to be invaluable tools in clinical epidemiology. Such registries have been very useful in some other branches of medicine (e.g., tumor registries, birth defect registries).

PATHOPHYSIOLOGY OF AUTISM: ETIOLOGY AND BRAIN MECHANISMS

ETIOLOGY

M. A. Spence

Response to NIH Questions

Question 1: What is the appropriate framework for studying autism? Are there multiple genetic loci and would this present insurmountable obstacles to

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249

? The consensus is that there must be heterogeneity (different genes being responsible in different families) within the autism spectrum disorders and this will undoubtedly make the search for etiologic factors more difficult. However, the goal is obtainable. Even if numerous loci contribute to autism and the sibling relative risk is therefore much lower than reported, it would take possibly 400 sib pairs and 300–400 marker loci to map the gene. That is a sample which could be achieved with international cooperation and an NIH-directed effort.

Question 2: Are there genetic models and/or genetic techniques that have been used successfully with other developmental disorders that may be applicable to autism? Family studies of affected pairs of relatives is definitely the method of choice for the time being as it avoids having to workup and classify borderline and problematic cases. Actually locating the responsible genetic loci after mapping to a general gene region is a *very difficult* task. This work would be aided by association tests and linkage disequilibrium and therefore these tests are also applicable but must be applied in special populations to be most informative. It is essential any time family data are collected to consider, ahead of time, the restrictions imposed by genetic methodology and whenever possible take those into account when designing the studies. Epidemiology has provided sufficiently accurate estimates of the prevalence for the genetic analyses but also contributes by providing quality data on subtypes and comorbid conditions. Note also the query under Unresolved Issues regarding evaluating the need for a large twin study. (See recommendations for specific research below.)

Question 3: Do genetic and environmental factors act through common mechanisms to trigger the pathophysiology associated with autism? It is not premature to investigate gene–environment interactions. In fact, there was a strong consensus at the meeting that there must be relevant environmental factors even in the face of the genetic evidence. Even monozygotic (MZ, identical) twin pairs are not always concordant for autism (do not both always have or not have autism). Immune irregularities also suggest a role for pathogens, and findings of minor physical anomalies suggest a delay or disruption in early development. Given the complexity of autism from a clinical neurologic perspective, it appears highly likely that there is a common pathophysiologic sequence that is triggered in various ways by epigenetic and/or environmental factors. Clear identification of subtypes and rigorous studies on defining comorbid conditions will be a major first step in research in this area. Longitudinal studies are also an essential means of obtaining critical information regarding gene–environment interactions. Additional research on environmental causes or precipitants is clearly warranted.

The natural course of the autism spectrum disorders and the early predictors of later diagnosis are not yet well identified and understood. There

is a sense that studies in these areas are making progress and should be encouraged for a variety of reasons. An important contribution of these studies will be a better understanding of the developmental stages and critical times in the course of the disorders. This will be invaluable in understanding gene–environment interactions.

Question 4: How can the genetic basis for autism be confirmed and further identified? We are definitely ready to test gene linkage hypotheses by initiating a formal genome search focused primarily on multiplex families (see below). However, there is no reason why these genetic family studies could not also serve as the primary vehicle for obtaining all the essential clinical and treatment data possible on the affected individuals and common relevant variables on the relatives. This procedure would avoid the expense of mounting both genetic and other studies and also improve measurably the quality of the genetic analyses. This multidisciplinary approach is exactly the one that has proven so effective in other complex diseases (such as breast cancer) which have seen quantum leaps in knowledge in the past couple of years.

Recommendations of the Working Group on Etiology

The search for the etiology (underlying causes) of the autism spectrum disorders is intertwined with research on diagnosis, pathophysiology, and treatment. Information from each of these areas helps to point the way toward possible causes. In turn, each of these other areas awaits discovery of the biological marker(s) for autism needed to expand and confirm its own findings. The working group on etiology recommends the following research priorities.

1. Genetic Analyses. There was remarkable consensus at the meeting that autism is a genetic condition. Mapping studies should be undertaken to identify the genetic loci that contribute directly to the disorder. The familial relative risks are sufficiently large to indicate the action of genetic factors and estimates of the number of loci involved are on the order of 3–6. For those reasons it was suggested that studies be initiated using affected pairs of relatives methodology (probably sib pairs, i.e., pairs of siblings). The information from the Human Genome Project, namely, the human fine-resolution genetic map, is exactly the required information to plan and carry out a successful genome search for loci contributing to the autism spectrum disorders. In addition, the parallel development of designated experimental organism maps and their sequencing will also contribute if/when appropriate animal models for specific aspects of the spectrum are developed. However, there are several important concerns and issues to be addressed if this research is to be sufficiently rigorous to have a reasonable chance of success, especially in view of the expected genetic heterogeneity (different genes being responsible in different families): (a) A very strictly applied set of diagnostic and sociodemographic criteria is essential in selecting individuals for these studies. Research on standardization of screening and diagnostic techniques and definitions of subtypes is directly relevant here. (b) The best strategy for ascertainment (identification of subjects) is to focus on multiplex families (more than one affected individual in the same family who independently meet criteria for diagnosis) to minimize the problems with uncertain or borderline cases. (c) From the beginning, the available sample should be split into two subsamples, one for detecting the loci and another for validating the results. These families are sufficiently rare that if most are inadvertently used to detect the linkage it will not be possible to confirm the results without an undue time delay. (d) Careful consideration must be given to the design of the study because of the vast amount of work necessary to have sufficient genetic markers to complete a thorough genome search (which is required in the absence of good candidate genes). Therefore, the design will need to carefully weigh the three points above as well as the possibility of collecting parents and single cases (trios) for haplotype relative risk analyses which will be essential in finding the specific loci responsible after identifying a region of the genome through linkage analyses.

2. *Family Studies*. It is important to emphasize that studies of family members have roles in addition to the linkage studies discussed above. For example, the gender ratio difference in autism is striking and families of females with autism may provide clues for understanding this difference if carefully studied. The following are other possibilities, but not an exhaustive list: (a) Geneticists should be included in planning any family studies since some (not all) of the more rigorous genetic analyses require that families be identified in a manner that can be specified in the likelihood equations. This ascertainment must be defined *before* the families are selected for study. By including this prior planning, families will be eligible for inclusion in the genetic studies as well as providing data for other purposes. (b) Family studies provide a unique opportunity to test whether or not the defined subtypes (e.g., clinical, drug response, language acquisition) also point to detectable differences in siblings and parents, recurrence risk (genetic subgroups), or other important features. Several areas of research, including neurochemistry and language studies, already have data indicating that some but not all families have nonautistic members who also display detectable differences when studied.

3. *Epidemiological Studies*. Current estimates of prevalence of autism are sufficient for the genetic analyses and no further precision is required at this time. However, the epidemiology approach would provide invaluable

information in the definition of subtypes, comorbid conditions, and documentation of the range of variable expression of all of the spectrum disorders through the correct sampling and statistical analyses of the required data. Possible environmental causes or precipitants of autism may also be revealed. UNOC-CAP data would be useful in this regard.

4. *Statistical Issues:* Throughout the conference, there were discussions about the need for statistical rigor in diagnosis, defining subtypes, identifying risk factors, designing studies, and determining sample sizes. All the points raised are essential for the quality of the data and directly affect the genetic studies. These issues are discussed elsewhere in the report (cf. Statistics below), but should also be considered in any discussion of genetics.

5. *Animal Models*. Research in animal models, as with all good research, should be hypothesis driven (i.e., designed to answer a specific, testable question). However, there are now several good reasons why time should be spent considering appropriate animal models with the possibility of using them to move the research forward more quickly. For many of the biological variables, and quite possibly for the behavioral variables (such as cognition), study in animal models permits rapid breeding schemes which lead directly to estimates of heritability and number of involved loci. Added to that now is the direct comparability of the genetic maps among organisms (e.g., mouse and man) which facilitates the identification of genes in an experimental organism and their immediate location in man. There are two recent examples of this approach. First is the cloning of an obesity gene in the mouse and the identification of the human homolog the same day by computer search. Although no one knows the role of this locus in human obesity, there is now a specific candidate gene for etiology and pathophysiology studies. Second is the recent request for applications for studies to develop the genetic map in the rat issued because the investigators in hypertension are very close to mapping a number of loci that have significant affects in the different forms of the disease. The hope again is to move directly from the rat results to test for the importance of the homologous regions in the human genome.

6. *Unresolved Issues*. There are several additional areas of possible future research that have been identified in the discussions of directions for genetic studies: (a) The role of immune factors in the autism spectrum disorders is not resolved and warrants sufficient studies to clarify the situation. There may be indications that serotonin level and the immune response are correlated and this should be confirmed or denied as soon as possible. (b) MZ (identical) twins provide a unique experiment since they must share all their genes but are well documented to differ in important environmental factors including prenatal and developmental stochastic processes. The comparison of twins either discordant (one with autism, one

without) or concordant (both with autism) could provide insight into both genetic and environmental factors of importance. An issue for discussion is whether or not it is cost-effective and scientifically useful to mount a large epidemiologic twin study to identify a sample of MZ and DZ twins for study. There are very few twin pairs in the literature, most from European studies and single case reports (U.S.). Should the study be done in the United States or is an international study needed? (c) Numerous cases of autism are reported with chromosomal variants (trisomy, translocations, etc.) but many of these were identified before the high resolution banding studies were available and before breakpoints could be cloned and uniquely identified. These cases should be collected and the newer studies performed to assess whether or not there are specific chromosome changes involved with the clinical features of this disorder. (d) Linkage disequilibrium is utilized via haplotype sharing and association studies to more precisely pinpoint the location of genes than is possible through linkage studies. To successfully apply this approach it is necessary to utilize populations that are genetic isolates or those known to have descended from a few founders (i.e., Finland). Are there identifiable populations that fit these requirements in which autism spectrum disorders are documented to occur, and where the prevalence of the disorders would warrant initiating such studies?

BRAIN MECHANISMS

M. Denckla

Responses to NIH Questions

Question 1: What brain regions and functional pathways appear to be affected in autism? What key steps in development (timing, type, and loci) that are particularly sensitive to genetic or environmental insults are likely to be associated with autism? Research studies in autism in the last 15 years using a wide range of technologies have provided evidence of a biological basis for autism. Information from neuropathology indicates that there may be abnormalities in the amygdala, hippocampus, septum, mamillary bodies, and the cerebellum. Autistic brains are slightly larger and heavier. (Clinical measures also indicate a larger than normal head circumference.) In the limbic system, there is an excess of cells and they are too small. The neurons themselves seem developmentally immature with a truncation in the development of their dendritic trees, which provide the basis for connections between neurons. Moreover, Purkinje cells are affected in a widespread fashion in the cerebellum. The anatomic differences found are

consistent with a developmental curtailment that takes place at some point earlier than 30 weeks gestation (before birth). The neuropathologic findings are reasonably consistent and appear to dovetail with the lesion studies in primates. Exactly which findings are universal in autism and specific *only* to autism remain to be demonstrated.

Contemporary imaging research coupled with sophisticated neuropsychologic tools also offers exciting research possibilities for studying brain structure and function in vivo, particularly as new technology in both image acquisition and image analysis is developed. As with all research in autism, standardized diagnosis and control for age, gender, degree of mental retardation, language, and comorbid conditions are essential in interpreting these findings. The identification of reliably occurring subtypes and subgroups will be absolutely critical with all methodologies, as we can expect that a variety of brain structures and mechanisms may exist for subtypes with differing etiologies.

Across methodologies, studies reveal both higher and lower order areas that are dysfunctional. Neuropsychological studies have been uniform in finding deficits in certain aspects of higher order cognitive functions, including abstract and pragmatic language, encoding of complex information, and executive (frontal) functions. Other aspects of higher order cognitive functions, particularly those involved in verbal syntax and visuospatial organization are often spared in higher functioning individuals. Deficits in certain aspects of attentional functioning also are common and lower functioning persons with autism may also exhibit severe receptive and expressive language impairments, including mutism and a deficit in declarative memory. In contrast, rote memory often is intact. Evoked potential studies have also provided evidence of abnormalities in late information processing related to both frontal and parietal cortex. In contrast, evoked potential studies of early and midlatency potentials have demonstrated intact function in some subcortical areas. This neurophysiologic profile has been replicated with ocular motor, oculovestibular, and postural physiology methodology.

However, in terms of the timing, type, and locus of the originating abnormality in autism, the data from neuropathology suggest that other areas remote from the neocortex may be the beginning of the pathophysiological cascade. The universal impairment in social cognition found in neuropsychologic studies of autism suggests involvement of certain brain regions known to mediate social and emotional behavior, namely, regions of the limbic system, such as the amygdala and orbital frontal cortex. Animal research indicates that limbic lesions my cause secondary dysfunction in the neocortex. There is precedence in other diseases for this pathway, for example, progressive supernuclear palsy (PSP). Autopsy results in PSP show defects in the upper brain stem. However, PET scans in vivo show ntal area *dysfunction*. Frontal area functions are closer to the surface and have an amplified effect on scans. The upper brain stem may not properly activate the frontal area. What is most obvious in in vivo imaging may not necessarily reflect the basic defect.

Taken together, the available evidence in autism suggests that, although certain aspects of brain functioning are often spared in autism, the syndrome nevertheless involves widespread brain dysfunction at both the cortical and subcortical levels. The originating site of the brain injury has not been identified. The competition of "top down" and "bottom up" hypotheses for the pathophysiological cascade in autistic development provides a fruitful area for future research.

At the subcellular level, neurochemistry research has provided consistent evidence of an elevation in a major neurotransmitter, serotonin, which affects potentiation at synapses and may play a role in the development of the nervous system. In terms of pathophysiology, it appears that there is a shared expression of a mutant gene in brain and platelet with respect to hyperserotonemia. Genetic analysis of the primary structure of the relevant neurochemicals is likely to be important for autism which has a sibling recurrence rate 4 to 10 times higher than that of insulin-dependent diabetes mellitus (IDDM) which has been found to have a genetic basis. Identified mutations could provide the first useful animal models of autism by homology, although animals will have a more limited behavioral repertoire.

Question 2: What behaviors observed in autism are consistent with the neuroanatomic findings? Neuropsychological animal and human studies have demonstrated the key roles that some of the brain areas affected in autism may play, particularly in social/emotional development. Studies of the amygdala indicate its importance in recognition of the affective (emotional) significance of stimuli, in social stimulus-reward associations that allow understanding of the connections between behaviors and their consequences, in perception of body movements and eye gaze direction, in orienting toward social stimuli, and, together with the hippocampus, its role in long-term memory. Representation of action plans, motor planning and execution, and working memory are associated with the frontal lobe and the basal ganglia. There have been reports of late-onset symptoms in the frontostriatal system in monkeys who experienced early limbic system lesions. Rapid shifts in attention and modulation of sensory input have been associated with the cerebellum. Neurochemical strategies could be used to study specific behaviors in response to specific neurochemicals that are most likely to have an impact on the development of those regions thought to be involved in autism.

In terms of etiology, much debate has occurred regarding the identification of a single primary deficit at the cognitive level. Rather than focusing on the identification of a primary brain structure that is abnormal, it is important to recognize that multiple structures at multiple levels of the neuroaxis have clearly been implicated and all these structures participate in the neural systems that influence behavior. The pathophysiology of autism, or the structural and functional abnormalities of the brain and how precisely they result in the abnormal behavior of autism is far more complex than what brain structures or neurochemicals are involved. Each level of analysis is highly complex and, at present, only pieces of this puzzle in autism have been identified.

Question 3: What are the critical influences that the process of development brings to the design of experiments and the interpretation of findings? Development clearly changes the outward expression of the signs and symptoms of autism. In addition, the changing signs and symptoms of autism must be compared to the changing backdrop of normal development in which the outward expression of normal abilities are also changing. In addition to variability associated with aging is the variability that occurs in normal humans in relation to general intellect and, in some cases, also gender and, in autism, in relation to severity of the disorder and developmental timing of onset, that is, congenital (at birth) or regression after apparently normal development. In assessing clinical functions, this means that different tests will be needed for different age- and ability-level individuals and that comparison groups must be matched on these relevant variables. With neurobiologic measures, these same variables of age, level of function, gender, and onset have a major impact and must be carefully considered in defining normative values and deviations from the norm. Several such methods including imaging and electrophysiologic cohesion measures have demonstrated that there are important and predictable changes in the relationships between measurements in different regions over the course of normal development. These factors require as careful attention to the selection of control subjects as to the rigor of diagnosis of autism.

Primate models also illustrate the importance of the role of development in the pathophysiologic cascade. Depending on the exact timing of the lesion, early injury to one part of the brain may result in later deficits in that part or in another part of the brain remote from the site of the original lesion. With certain known animal brain lesions, there is not much difficulty as an infant but there is significant social and working memory difficulty in adulthood. How profound the autistic-like behaviors are in monkeys depends on how early in the developmental process the brain lesions were made. Only through longitudinal animal studies can one find out what was primary and what was secondary. Longitudinal as opposed to cross-sectional studies could indicate whether subcortical findings are earlier and cortical findings are secondary to those deficits or vice versa.

Question 4: Does the available evidence suggest that there are prenatal/perinatal events associated with autism? If so, are they specific to autism, are they likely to be causal, and can they be used for clinical prognosis and the development of treatment strategies? The available evidence suggests that there may be more problems in pregnancy or at birth, or more health problems immediately after birth in children with autism than in control families. Risk factors such as maternal age, prematurity, bleeding in pregnancy, toxemia, viral infection or exposure, and poor vigor in the neonatal period have been studied. However, there is little evidence that these problems are consistent across cases of autism or that they are specific to autism since they are also found in disorders such as dyslexia or developmental language disabilities. Such problems do not predict to later autism, nor do they appear to be related to asphyxia. These factors do not appear to cause autism, but may be reflections that fetal or neonatal development was compromised in some way.

Recommendations of the Working Group on Brain Mechanisms

1. Investigation of brain structures in vivo with imaging methods is a major priority. At present, there are few data on most brain structures in autism. Cross-sectional, whole-brain studies at various ages are an essential first step in defining the relevant neuroanatomic focus for later studies. Functional MRI is a developing method that provides an opportunity for looking at the function of neural circuits without the hazards of radiation inherent to PET scans. Longitudinal studies in this area may be premature at this time until the rapidly changing technology stabilizes to allow for consistent measurements across time.

2. The use of the technology of neuropsychology, both human and primate, can help sort out specific aspects of clinical functioning and refine knowledge of hypothesized relationships between cognitive deficits and behavioral difficulties. Methodological developments in this research area are also needed to define the testing paradigms necessary for nuclear magnetic resonance imaging of the functional variety.

3. To expand knowledge of neuroanatomical findings, the need for access to a user-friendly brain bank was emphasized. Use of such a brain bank would lead to a greater number of appropriately age-, gender-, and cognitive-level matched controls being made available for study. Appropriate allocation of brain material to many different disciplines would allow the fuller use of postmortem brain samples for the study of specific anatomy and contribute to the urgently needed refinement of quantitative research methods for analysis. It would also permit staining of circuits that

are associated with certain neurotransmitter pathways for use in [illegible]etically driven studies about the action of protein.

4. Studies of primary structure of relevant neurochemicals by genetic analysis are needed, since genetic study is mainly a tool to study neurochemicals in terms of determining which, when, and where proteins are expressed in the developing nervous system. For example, proteins involved in the development of neurons shown to be abnormal from postmortem studies can be examined by DNA analysis available from blood or saliva from well-characterized patients who may be followed prospectively.

5. In an effort to identify key mechanisms in the pathogenesis of autism, studies of nerve growth and nerve growth migratory substances important for the modeling and remodeling of basic architectonics of certain centers of the human brain particularly important for language and social skills could be carried out. For example, family histories of affective disorder have been found in autism. In affective disorder, abnormalities have been identified in cell structure immediately adjacent to the inner surface of the cell membrane. This is also the site of action of neuronal growth factors, such as Growth Associated Protein, which guide the growth of developing neurons. This suggests an overlap or shared abnormal factor at the neurobiologic level in the regulation of brain membrane development in autism and affective disorder, particularly with regard to the inner membrane associated cytoskeleton. The association between autism and tuberous sclerosis may also be a particularly fruitful one in understanding the pathogenesis of both disorders. Research is also urgently needed that distinguishes two different developmental trajectories in autism, the one congenital (from birth) and the other characterized by apparently normal development followed by regression and onset of autism.

6. Two important considerations for future research include the need for developmental norms for many new methodologies and consideration of norms in relation to IQ, gender, and race. Much of what is known about brain function and neuropathology is based on acquired brain damage in adults. If neurobiologic strategies are to be effective in correcting structural abnormalities of the brain, then noninvasive technology for the study of higher order cognitive abilities and their neural substrate should be employed over the course of development. The majority opinion was that newer functional magnetic resonance imaging will displace PET scans for activation studies, particularly once the enlarged windows of brain visualization are perfected.

With regard to special considerations for such research, it is particularly important that normative data across the age span be accumulated with these new and more sophisticated methodologies for studying the brain such as volumetric MRI morphometry, functional imaging, and MR

254

spectroscopy. It is also important to define normal in consideration of subject variables likely to have a major impact on neuronal organization including age, IQ (particularly Verbal IQ), gender, and race (especially in studies of infants and toddlers where the acquisition of milestones varies by race). It is also important that controls be chosen and matched as carefully as the autistic subjects and that they too be thoroughly assessed for evidence of current and past history of neurologic and psychiatric disorders as well as for family history status. Use of structured instruments for these purposes should be routine.

7. Reports of abnormalities in higher order motor abilities (praxis) and higher cortical sensory abilities are now emerging. These findings may provide a basis for some of the unexplained aspects of the clinical syndrome of autism such as the sensory distortions (e.g., the relative insensitivity to pain and the sensory sensitivities) and movement disorders. Apraxis could provide a neurologic explanation for the inability of very young autistic children to use sign language. Sensory and motor abnormalities may be quite disabling and intervention depends on a better understanding of the neurologic basis of these behavioral difficulties. There is a related need for research on movement and synchrony, building on some previous research in this area and on new findings in Parkinson's disease and autism.

8. Replicable findings and consistency across methodologies will only occur when well-standardized methods are used for diagnosis, choice of comparison groups that control for relevant demographic and developmental variables, standardized protocols for imaging and psychological testing, and well-quantified methods of analysis. Such standardization is needed for all levels of inquiry neuro/pathophysiologic/anatomic, and etiologic (genetic and environmental), but progress at one level will not automatically result in solving questions at another.

COMMUNICATION/SOCIAL/EMOTIONAL DEVELOPMENT

M. Sigman

Response to NIH Questions

Question 1: What aspects of communicative, social, and/or emotional function/dysfunction are specific and perhaps universal to autism spectrum disorders (core deficits)? There is strong evidence that the capacity to share attention and emotion with others is specifically and universally impaired in autism. This is manifested in less joint attention and social referencing

in young children with autism, less understanding of the feelings and thoughts of others in older children with autism, and less initiation of social behaviors and responsiveness to others' feelings at all ages. Simple recognition of facial expressions is intact in many individuals with autism. However, understanding that requires the person with autism to take the perspective of another is generally limited. This deficit is also manifested in serious difficulties in the functional use (pragmatics) of language by those individuals who acquire language skills. Understanding and assessment of these deficits raise particular problems in research with nonverbal children.

Question 2: What is known regarding the developmental trajectories of these communicative and social behaviors in persons with autism spectrum disorders? Only a few longitudinal studies of children with autism have been conducted. From cross-sectional studies, it is clear that some of the problems with joint attention and social referencing improve as children's cognitive abilities develop. However, the deficits are manifested in higher level social and language abilities. Longitudinal studies suggest that the capacity for joint attention is linked to language acquisition but the child's sociability predicts to gains in language skills. There is stability in individual differences in responsiveness to other's emotions and this is independent of level of intelligence. Additional longitudinal data are needed for most aspects of these children's verbal and nonverbal communication and socialization.

Question 3: What is known about the specific contributions of biological and environmental factors to these behaviors? Very little is known about how biological and environmental factors contribute to these deficits although emerging interventions in this area show promise of demonstrating environmental impact on outcome.

Question 4: By examining other neurodevelopmental disorders that have autistic-like behaviors (e.g., temporal lobe lesions in early childhood; certain seizure disorders that involve behaviors reminiscent of autism which disappear with treatment), what can be learned about the nature of autism and its core deficits? Most studies of children with autism compare their behaviors to those of heterogeneous groups of children with mental retardation or children with language disorders. These children do not share the social deficits of the children with autism. Some of the same methodologies have been used to compare children with seizure disorders and children with autism. In studies of samples with more serious seizure disorders, the children with seizures but not autism are equally impaired in all forms of nonverbal communication. Children with autism are the most impaired in joint attention and the least impaired in gestures used to regulate the behavior of others. The overlap of autism with seizure disorders, particularly seizure disorders that result in regression after normal development, is an important area

255

arch. In general, onset of autism after apparently normal early development is poorly understood and underresearched. The literature on frontal and temporal lobe lesions in both animals and humans is informative regarding the timing and type of lesions that affect social development. Preliminary data from animal studies also suggest the possibility of recovery from early brain injury with treatment. This research has implications for understanding plasticity and the efficacy of early interventions but is not yet directly applicable to autism.

Question 5: Are there new models, methodologies, and/or statistical/analytic techniques that show promise in answering these questions? These are proposed in the following section of Recommendations.

Recommendations of the Working Group on Communication/ Social/Emotional Development

Four types of studies are recommended by the working group to address the gaps identified above.

1. Longitudinal Studies Which Follow Children from Early Childhood to Middle Childhood and Then on to Adolescence. Studies that assess either identical communicative and social behaviors over time or different measurements of the same constructs are needed. It would be interesting to do these in tandem with measures of the child's relationships with family members as well as measures of neurological, sensory, and motor functioning. Groups of children should be followed who meet diagnostic criteria for autism as well as those who fit into the spectrum even if they do not meet all the diagnostic criteria. Outcome measures should be broadened to include social understanding, competence, and relationships assessed in a variety of ecologically appropriate situations such as home and school. Studies could be designed to address the following questions: (a) How persistent are early deficits? (b) What are the consequences of these deficits? (c) What are the mediators of variation in development? (d) What are the best predictors of which children will develop speech and of which children will lose speech and develop autism after apparently normal early language development (up to one third of children with autism)? (e) Is there secondary deprivation (i.e., because children are not biologically prepared to respond to and interact with their environment, their initial deficits are worsened because they do respond normally to the usual, growth-promoting experiences in their environments.)? How do different families, schools, and treatment facilities act to prevent the deprivation that results from the child's communicative and social deficits? Are there different outcomes in these cases? (f) Can communication/social subgroups be identified and how stable are these subgroups? (g) How do relations between sp deficits and neurological and cognitive functioning change with age? These studies could be linked to family studies so that the severity and persistence of deficits could be assessed in light of the characteristics of the families.

2. Studies of Early Diagnosis. Measures of early social and communicative functions (like imitation, joint attention, and social orientation) could be administered either to children with suspected developmental difficulties by parents, pediatricians, or day-care workers or to the infant siblings of children with autism. These children could then be followed to age 3–4 to validate the diagnoses.

3. Training Studies. Focused experimental interventions aimed at targeting abilities identified as specifically deficient in children with autism or predictive of later language and social skills could be carried out. These focused training studies would be short-term, intensive efforts to alter the child's communicative and social skills in a particular domain. They would supplement existing intervention or educational programs in which both experimental and comparison subjects are enrolled. Baseline measures would be made of neurological, sensory, motor, and cognitive functions. Training studies should be instituted during three age periods: *Early childhood*—Focus of intervention would be communicative skills, imitation skills, and/or affiliative behaviors. A multichannel approach (more than one type of sensory input, e.g., visual and auditory) could be used. *Middle childhood (nonverbal children)*—Preliminary research is needed to specify target behaviors since so few studies have attempted to identify deficits in communicative and social abilities in this age period. *Middle childhood to adolescence (verbal children)*—Focus of intervention would be understanding of the knowledge, beliefs, and feeling of the self and others.

4. Many individuals with autism lack speech and have limitations in gestural communication and in the use of augmentative communication systems. These problems areas may be caused or complicated by specific sensory difficulties and/or general motor or more specific motor/speech impairment. There is almost no systematic research in this area.

5. Multidisciplinary/Multicenter Studies. In some cases, multidisciplinary or multicenter investigations would be most effective. For example, in longitudinal studies of nonverbal and verbal communication skills, such investigations might allow examination of both biological and psychological development. This would make the research far more meaningful since continuity and change could be examined not only in each domain but also in the relations across domains. Longer term, multidisciplinary/multicenter investigations would also be necessary for linking family studies to longitudinal follow-ups of the autistic proband. Multicenter investigations would also be necessary when large samples are needed or to permit studies of [illegible]ized populations, for example, an early diagnosis study using a high-[illegible] sample, such as the infant siblings of children with autism, because of the small samples at any site.

MEDICAL INTERVENTION

D. Cohen

Responses to NIH Questions

Question 1: What are the most important goals for future research on medical interventions? There are two overriding objectives for future research on medical interventions: (a) rigorous evaluation of the effectiveness of currently available medical approaches to treatment; (b) facilitation of the creation of newer approaches to treatment that utilize advances in neuroscience, genetics, immunology, and other associated fields.

Evaluation of Treatment. The development and testing of biological interventions is a complex process that requires collaboration among clinicians and basic biological and behavioral scientists, including pharmacologists, psychologists, statisticians, and other neuroscientists. This process of clinical research should be embedded within suitable institutional contexts in which clinical care and investigation can be integrated, and in which there can be state of the art pharmacological and behavioral assessments of individuals with autism, at different phases of development and longitudinally. The infrastructure for this program includes the following components: (a) well-trained investigators familiar with the phenomenology and natural history of autism and with sophisticated methods of psychopharmacological research; (b) centers in which individuals with autism can be engaged in long-term biological research protocols, including inpatient and outpatient facilities, laboratories for biological and behavioral assessment, nursing and other staff for monitoring overall response, concurrent treatments, and support to assure long-term engagement of families in the research; (c) development and refinement of methodologies for assessment and for monitoring changes in various domains of functioning (including clinical rating procedures, behavioral observational methods, studies of functioning in important contexts, and laboratory-based assessments of cognition, attention, and other domains).

New Interventions. Advances in genetics, neuroscience, pharmacology, and other areas will continue to suggest new approaches to intervention. It is important to have investigators who are familiar with emerging areas of knowledge that may be relevant to autism (e.g., to new agents that are under

development). Also, there should be increased emphasis on [illegible] treatments that are specifically related to the core problems of autism. Currently, all medications used with individuals with autism were screened on test systems that are not specific for core symptoms of autism (e.g., screened in relation to antipsychotic and antidepressant potential). They have been used with children and with individuals with autism, in particular, as orphan indications. There is no current program aimed at developing and testing agents that may specifically relate to core areas of autistic disturbance—social and communicative impairments. The development of new approaches may be based on increasing understanding of the biological preconditions for social attachment, for example, the role of hormonal systems in modulating attachment, on important systems (e.g., dopaminergic, serotonergic, noradrenergic, and peptidergic systems and their interactions) that are implicated in specific classes of symptoms, and on genetic factors in behavioral development and disorder (as these are elucidated). In the future, the field of genetic pharmacology will play an increasingly important role. This field integrates molecular genetics and biological interventions that are specifically targeted at changing the expression of genes. With the localization of specific genes and characterization of gene products that may be related to autism, a new era of biological intervention will be opened.

Recommendations of the Working Group on Medical Intervention

The design of biological intervention studies is complicated by heterogeneity among individuals with autism, the importance of following the effect of treatments over long periods of time to determine changes in developmental course, the many different agents and procedures that are available for study, and questions of informed consent.

1. A task force is needed to study improved approaches to the evaluation of treatment to complement the standard, double-blind, placebo-controlled trials. In addition to efficacy, it is important to have studies that relate to clinical effectiveness for diverse groups of individuals with autism and over longer periods. New statistical methods for assessment of developmental course (e.g., individual growth curve analysis) may be helpful, and statisticians, methodologists, pharmacologists, parents, and clinicians need to be able to work together as teams to design suitable approaches.

2. The use of medication is rarely appropriate without other treatment approaches, including educational and behavioral interventions. This collaborative approach will provide maximum benefit for the patients and data normally collected in educational settings can prove useful in evaluating

ical interventions in "real life." Once efficacy of a single aspect of treatment (i.e., medical or behavioral) is demonstrated, drug by behavioral intervention interactions can be tested, but increases in sample sizes needed to test such effects tend to be exponential in numbers and cost.

3. Currently available assessment methodologies are perhaps more useful for baseline assessment than for monitoring change. New methods for assessment may be needed for "lower functioning" individuals and for carefully following the course of treatment response in various positive domains (learning, social, emotional, cognitive) as well as on target symptoms (e.g., aggression, activity level). Functioning in situations of daily living needs to be assessed as well as symptom severity. Short- and long-term side effects need to be monitored.

4. Response to treatment may help define new subtypes of individuals with autism and lead to further understanding of biological subtyping.

5. In the assessment of individuals with autism, epidemiological study of dietary history and current functioning is needed. Studies are needed of the unusual eating behavior of individuals with autism (e.g., limited diets, craving for or avoidance of certain foods, eating unusual substances) which has been shown in other disorders to lead to elevated levels of lead or reductions in important dietary components. Such study may also reveal possible undiagnosed symptoms related to diet (e.g., MSG or lactose intolerance) or reflect metabolic disorders.

6. Pharmacological interventions may require the use of more than one medication at a time. For example, the treatment of some nonautistic individuals with obsessive-compulsive disorder may sometimes be improved by the augmentation of a serotonin reuptake inhibitor with a neuroleptic (e.g., fluvoxamine + pimozide). Similar clinical needs are presented by some individuals with autism. Systematic research is needed to understand the biological and behavioral effects of multiple drug use.

7. A coordinated plan for supporting rigorous, sustained clinical research on biological interventions in autism is needed. This includes (a) facilitation of training programs and career development in the field of pediatric neuropsychopharmacology and associated fields of clinical research; (b) creation of centers for long-term engagement in the field of biological clinical research. This initiative might be undertaken as an expansion of the current NICHD networks on pediatric pharmacology. Centers involved in this work should have the capacity for rigorous behavioral and biological assessment, integration of biological and behavioral interventions, and long-term follow-up; (c) establishment of multicenter collaborations for evaluation of biological and behavioral interventions (in which studies can be implemented, monitored, and carefully assessed over longer periods of time, including short-term improvements as well as long-term effects on de-

velopmental course); (d) NIH should work with advocacy and professional organizations to increase the awareness of parents, professionals, and government about the importance of rigorous scientific research on biological interventions. This includes helping parents and advocates recognize the value of volunteering for studies (including placebo-controlled designs) that may delay the onset of treatment for certain individuals but will ultimately benefit the individual involved as well as the advancement of the field by promoting authentic scientific knowledge that can inform treatment.

SOCIAL AND BEHAVIORAL INTERVENTION

W. J. McIlvane

The term "behavioral" in this context is intended to distinguish the primary thrust of this research from that of biomedical studies. The term "behavioral" is not limited to research in the tradition of applied behavior analysis or behavior modification, but includes the study of human and animal behavior from a variety of theoretical and conceptual perspectives (e.g., developmental).

Response to NIH Questions

Question 1: What is known and what needs to be learned about the effectiveness of specific types of interventions for specific types of children with autism spectrum disorders? Although there is no cure, autism is treatable through educational interventions of various types. Early intervention may be particularly effective, presumably because of the plasticity of the neural systems at that time. When to initiate treatment, how intensive such treatment needs to be, and how long to continue it are important research questions to be addressed. It is also clear that persons of all ages and levels of ability can benefit from access to consistently available, proven treatment. It is also known, however, that treatment response is not uniform within the population. Although many children may be brought to the point of near-normal functioning, others are much less responsive to social/behavioral intervention programs.

Question 2: What important outcome variables have been well studied? What additional outcomes need to be considered? Treatment research has demonstrated the feasibility of fostering significant gains in language, social adjustment, preacademic and academic achievement, and other desirable outcomes. The focus of many studies has been on compliance and on speacademic or preacademic achievements. Promising research has also been done on the acquisition of functional abilities such as changes in spontaneous communication and adaptive, flexible behavior over time which are more meaningful than changes in measurements such as IQ. Assignment to regular classes as the criterion for successful outcome is often meaningless because it reflects local political and legal mandates more than individual child need or status. As in other domains of intervention research, studies are needed to determine the long-term effects of all interventions (particularly early intervention).

Question 3: What are the diagnostic, methodological, and statistical issues that must be addressed in future behavioral and social intervention research? Research thus far has demonstrated that intervention, and particularly early intervention, offers significant hope for lessening the effects of autism. Many questions remain unanswered, however. Research is needed that uses robust experimental designs to evaluate and *compare* various approaches to treatment. Methods are needed that (a) involve random assignment to different treatment conditions; (b) use standard intervention protocols that capture a wide range of skills and symptoms, under both laboratory and "real life" situations; (c) make use of outside evaluators who are not invested in the outcome of the research; (d) assure high compliance with the defined treatment protocols to be sure that the intervention as designed is actually and consistently implemented; and (e) use longitudinal designs that evaluate treatment effects, both during the treatment itself, and at set points after the intervention has been accomplished.

The social/behavioral working group felt the need to identify (and perhaps to develop) research methods that would increase the likelihood that families would agree to the participation of their children in research studies. Newer statistical approaches (e.g., individual growth curve analyses) were encouraged. In particular, the working group felt that it was essential to distill a set of outcome measures that would have broad appeal for evaluating treatment approaches. While there was recognition of the significant potential for controversy in this area, it was felt that the problem could be managed and a reasonable set of measures might emerge if a broad constituency was involved in the development effort.

Question 4: What are the aspects of social policy that facilitate or impede research in this area? Recent developments in social policy, particularly the movement towards inclusion of individuals with autism (as well as other disabilities) in community schools, recreation, employment, and other activities of daily life are very influential on the ability to accomplish high-quality intervention research. While the goals of the inclusion movement were acknowledged and supported, there was considerable agreement that intervention should respond first to the needs of the individual with autism

(and his/her family), tailoring the approach to make it possible for each individual to achieve his/her full potential.

Some concern was also expressed that social policy advancement was needed to streamline the process of obtaining human studies approval for intervention studies. Although the committee was clearly aware of and duly concerned about the need to protect individuals with autism and their families in accomplishing research studies, the growing requirements for sometimes numerous, largely redundant reviews by multiple human subject review boards were seen as a possible obstacle in accomplishing certain types of intervention studies.

Recommendations of the Working Group on Social/Behavioral Intervention

1. A high priority for future research is studies that relate characteristics of individuals (or group subtypes) to treatment outcomes. Outcomes depend upon the interaction of the characteristics of the individual with the characteristics of the treatment approach. What works for one child may be ineffective or even counterproductive for another. Both categorical and dimensional approaches were discussed and may prove appropriate for defining such characteristics.

2. Too little attention has been given to environments and to the interaction of affected persons with aspects of their environments that typically affect child outcome. Particularly needed are studies of parent–child and sibling–sibling interaction over time, and of the effects of physical environments, behavioral modeling, relationships, exposure to speech, and technology such as computers that could contribute to more or less successful outcomes.

3. Another priority is research that would define the critical features of effective intervention programs for persons at different ages. At the present time, data have been presented regarding effective intervention "packages." It is critical to determine what aspects of the particular program, including family variables, and what intensity and duration of intervention are needed for successful outcomes at various child/adult ages. Post hoc testing to generate hypotheses for future research for targeting interventions is needed as well as hypothesis-driven prospective studies.

4. Collaborative, multisite projects appear necessary to obtain an adequate sample of children and intervention programs to assess subject by treatment interaction (i.e., what works best for which children) and to determine if the treatment can be effective in other treatment sites and samples with different persons implementing them.

259

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As principles of effective treatment are increasingly well defined, research is needed to ascertain how best to encourage transfer of that learning for individual children (generalization) from clinic to home, home to school, school to community.

6. It is clear that all persons with autism are not currently receiving services based on the most advanced knowledge available. Mechanisms should be devised to expedite rapid transfer of research into practice.

7. There was agreement that maximally effective intervention would have to be a multidisciplinary effort. Without diminishing the value of well-focused individual research initiatives, high priority was accorded to research projects that could demonstrate truly effective, productive interdisciplinary interactions. For example, although methods derived from applied behavior analysis were acknowledged as especially effective in treating autism, it was thought that incorporating perspectives from developmental psychology and neuropsychology, among other disciplines, might enhance the effectiveness and acceptability of treatment methodologies. The importance of so-called "state" variables (nutritional status, drug status, etc.) was also deemed critical, and research to document state–treatment variable interactions was recommended. Implicit in these recommendations is the need for an organizing framework that is broad enough to incorporate inputs from the many disciplines that can make a helpful contribution to solving the problems of autism spectrum disorders.

8. If early intervention does substantially alter growth trajectories, as it appears, follow-up research will be needed to confirm that intervention does in fact produce lasting beneficial changes that would not be achievable without that intervention. Studies should be designed to ensure that the gains are not an artifact of subject selection or maturation. Some studies may incorporate imaging or other techniques that demonstrate potential biological (i.e., evidence of neuroplasticity) as well as behavioral change, particularly as higher-speed imaging techniques become available.

BIOSTATISTICAL RECOMMENDATIONS

H. C. Kraemer

Little more can be learned either from cross-sectional or from retrospective research on many key issues in autism. Autism is a developmental disorder, with very early onset, and is chronic over the lifetime of the patient. There is a serious need to understand what are the stable *traits* of patients and to distinguish these from what are the *stages* of the disorder, and to distinguish both traits and stages from *states* and *random variation*.

To do this requires prospective, longitudinal studies. The problem is that such studies are costly in terms both of research time and research cost.

New statistical methodologies are currently emerging to make such studies more informative as well as most cost-effective. Individual growth models have been mentioned frequently in this report, for example. Such models acknowledge both the consistant individual differences (traits) within groups of persons with autism and those differences expressed in different trajectories (stages). Moreover, such approaches are much more tolerant of unequal follow-up times, or irregular scheduling of follow-up times, and are much more robust to the less than perfect reliability of many available and pertinent outcome measures.

To reduce both time and cost of such studies as well, accelerated lifetime sampling methods are available, where subjects are entered into study at different ages and followed for some period of time (say 5 years), in such a way that age span over which different subjects are followed overlap each other. One can, by such methods, accumulate a depiction of the general growth patterns over the first 20 years of life, for example, using only 5 years of follow-up per patient.

There are many other such strategies either currently known but seldom used, or under current development, or that could be developed that are particularly appropriate to the study of this disorder. Development and dissemination of such methodological strategies might be supported for researchers in the field.

It is known that some persons with autism are high- and some low-functioning; that some are mute and some vocal; that some respond to a certain treatment and some not. Dr. Grandin made the point most strongly that there is a great degree of heterogeneity among persons with autism that is not well understood, and sometimes not even acknowledged.

Identification of subtypes is important, that is, subgroups of those appropriately diagnosed with autism who may have different etiologies, different course, and/or different response to treatment. If such subtypes exist, they are currently being lumped into one group. The heterogeneity so introduced by "lumping" diminishes the power to detect any signals, whether they be the genetic basis of the disorder, risk factors for the disorder, discrimination between persons with autism and those with normally developed brain structure and function, or treatment efficacy/effectiveness. It is crucial to future research and development of knowledge that, if such subtypes really exist, they be identified. On the other hand, we do not *know* the boundaries of autism or any subtype of autism. For example, we can reliably distinguish autism, Rett syndrome, and childhood disintegrative disorders (CDD), but are these simply different expressions of the same disorder or of different disorders (again, different etiologies, course, or ment response)? It should be remembered that before the organism for syphilis was identified, it was thought that there were multiple different diseases depending on which organ system was primarily affected. To "split" when there is no valid reason to do so may also undermine a research study's results. The search for a biological marker(s) is critical here.

Comorbidities are yet another problematic source of heterogeneity among persons with autism. Some comorbidities are random—one might have a cold and corns at the same time, and they have nothing to do with each other. Some comorbidities may be different expressions of the same disorder, or one disorder might lead to another. In such cases, these are not necessarily separate disorders, but perhaps different manifestations of the same disorder, or different stages of a single disorder. Some comorbidities are indeed separate but related disorders, due to linked genes or related environmental effects, or with common risk factors, some causal, some not. When comorbidity exists, each disorder may or may not affect the success of treatment of the other.

Should we "lump" or should we "split"? Each is appropriate in different situations, and whichever is inappropriate will compromise research success in understanding autism. It is essential to gain a greater understanding of the heterogeneities among persons with autism, and a recognition of which sources of heterogenaity are clinically important and which are not, for these issues have major repercussions in terms of research design and research success.

Another recurrent theme has been that of fostering closer connections between research efforts and real life. Patients, parents of patients, as well as interest and support groups should be involved in clinical research studies, both for the traditional purposes of fund raising and help with patient recruitment, but also to help researchers formulate the questions most important to patients. Along this line: (a) We should increase emphasis on long-term effectiveness rather than short-term efficacy studies. (b) We should reconsider the appropriate choice of control group (When is a placebo group the appropriate choice?), which may not be the same in all studies. (c) We should include consideration of both financial and emotional cost to families as outcomes in clinical trials as well as quality of life measures.

With the difficulty of defining samples that control for relevant variables and the severity and impact of autism, there should be special emphasis on high quality research, for example, diagnosis, sampling, measurement, design, and power. Frequently, the argument is made in the opposite direction: Since the issues are so important, we should allow researchers more latitude in designing and executing their studies. It is important to realize that funding poorly designed research is not only a waste of time and money that might better have been invested elsewhere but the

results may actually mislead the research field and m[illegible]inform the clinicians working with patients with autism.

Moreover, it may well be that new modes of research collaboration need to be forged. Multisite trials are certainly one such example. Collegial agreements between independent research centers studying autism that a finding at one site should immediately be followed by an attempt to replicate and confirm that finding at another site, is another example. Autism registries, brain banks, and gene banks have also been mentioned as possible resources to foster excellent and cost-effective research efforts.

GENERAL RECOMMENDATIONS REGARDING RESEARCH IN AUTISM

1. A conference similar to this one should be convened in 2 or 3 years to assess the efforts and progress made.

2. The four funding agencies are strongly encouraged to coordinate support for autism research to help promote large-scale projects that would be difficult to fund within a particular institute.

3. To ensure a fair review of clinical research on developmental topics, at least one study section focused on the value and special needs of clinical research is needed.

4. Although coordinated, multisite investigations are clearly needed when large samples or immediate replicability is required, support for hypothesis-driven smaller studies by individual investigators should also continue to be encouraged.

5. Ethical issues of informed consent, withholding treatment in placebo/control designs, random assignment to different treatments, and impact of intrusive research and clinical procedures on this vulnerable population merit serious discussion with scientists, parents, self-advocates, and legal advisers.

ACKNOWLEDGMENTS

The authors and conference participants gratefully acknowledge the dedication of the Autism Society of America that initiated the NIH Autism conference, and of the Autism National Committee that endorsed it; the Congressional leadership that makes this and all NIH research possible; the tireless efforts of the NIH Autism Inter-Institute Conference Coordinating Committee members, especially Dr. Duane Alexander, conference convener, who made the meetings a reality; and the scholarship and open-

261

ness of the Autism Working Group whose disparate views are synthesized in this report and these summary papers. Finally, we thank those persons with autism and their families from whom we learn through research and for whom we toil.

In addition to the reporters and authors of summary papers the NIH Autism Working Group included: Pasquale Accardo,[3] Duane Alexander,[2] Patricia Amos, Edward Bedford, Ira Cohen, Judith Cooper,[4] Barbara Cutler, Felix de la Cruz,[4] Rebecca Del Carmen,[4] Ellen Feiforck, Deborah Fein, Carl Feinstein, Susan Folstein, B. J. Freeman, Janina Galler,[3] Peter Gerhardt, C. T. Gordon, Zach W. Hall, James C. Harris,[3] Eric Hollander, Jerri Jacobs, Helena C. Kraemer,[3] Peter Jensen,[4] Michele Jones, Gary P. Kaplan, Connie Kasari, James F. Kavanagh,[4] Sandra Kownacki, Linda Kunce, Michael Lamb,[3] Rebecca Landa, Brenda Lee, Eric London, Lee Marcus, Joyce E. Mauk,[3] Audrey McMahon, Sakkubai Naidu, Karin Nelson,[3] Ralph Nitkin, Susan Pratt, Isabelle Rapin,[3] Judith Rapoport,[3] Joanne Roberts, Patricia Rodier, Jacquelyn Rosen, Elizabeth Roth, Jamie B. Ruppmann, Gene Sackett,[3] Bryna Siegel, Gloria Simpson,[3] James B. Snow, Donna Spiker, Giovanna Spinella, Beth Sposato, Travis I. Thompson,[3] Lynn Waterhouse, Harry H. Wright,[3] Sumner J. Yaffe, Andrew Zimmerman,[3] Louise Zingeser, and Veronica Zysk.

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Original research

Welcome paulkim

Articles Volume 350, Number 9080, 13 September 1997

Previous ‹

› Next

A case-control study of measles vaccination and inflammatory bowel disease

*Mark Feeney, Andrew Clegg, Paul Winwood, Jonathon Snook, for the East Dorset Gastroenterology Group**

**Listed at the end of the paper*

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Summary

Background The cause of inflammatory bowel disease (IBD) remains to be established. Evidence has linked measles infection in early childhood with the subsequent risk of developing IBD, particularly Crohn's disease. A cohort study raised the possibility that immunisation with live attenuated measles vaccine, which induces active immunity to measles infection, might also predispose to the later development of IBD, provoking concerns about the safety of the vaccine.

Method We report a case-control study of 140 patients with IBD (including 83 with Crohn's disease) born in or after 1968, and 280 controls matched for age, sex and general practitioner (GP) area, designed to assess the influence of measles vaccination on later development of IBD. Documentary evidence of childhood vaccination history was sought from GP and community health records.

Findings Crude measles vaccination rates were 56·4% in patients with IBD and 57·1% among controls. Matched odds ratios for measles vaccination were 1·08 (95% CI 0·62-1·88) in patients with Crohn's disease, 0·84 (0·44-1·58) in patients with ulcerative colitis, and 0·97 (0·64-1·47) in all patients with IBD.

Interpretation These findings provide no support for the hypothesis that measles vaccination in childhood predisposes to the later development of either IBD overall or Crohn's disease in particular.

Lancet 1997; 350: 764-66

Previous ‹

› Next

BMJ 1998;316:561 (14 February)

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Medicine and the media

Media dents confidence in MMR vaccine

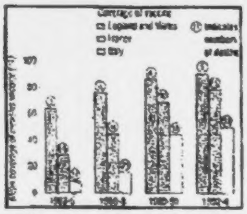
Norman Begg and colleagues assess how adverse publicity damages vaccination programmes

Once again the media have succeeded in denting parents' confidence in childhood immunisation. Coverage of the first dose of MMR vaccine in the United Kingdom fell last quarter after adverse publicity in the press linking MMR vaccine to Crohn's disease (*Communicable Disease Report* 1998;8:41).

The national fall in vaccine coverage was 1%, although in 25 (20%) districts and health boards coverage fell by 2% or more. Altogether, about 2000 fewer children were vaccinated than in the previous quarter. The weight of scientific evidence has subsequently shown that these media reports were unfounded (*BMJ* 1998;316:166) and that there is no causal link between MMR vaccine and Crohn's disease. Nevertheless, the damage to parents' confidence has been done. The press rarely give much prominence to negative findings that exonerate the safety of a medical intervention. As Jonathan Swift put it: "Falsehood flies and truth comes limping after; so that when men come to be undeceived it is too late; the jest is over and the tale has had its effect."

Adverse media reporting has previously affected coverage of MMR vaccine in other countries, notably Denmark, where coverage dropped to a record low in 1993 after a television programme attacking MMR vaccination. Unrepentant, the same TV channel broadcast another unbalanced anti-vaccination programme last November.

What the journalists do not report is that measles, mumps, and rubella still cause substantial morbidity in developed countries. Where vaccine coverage is low the incidence of disease is high. Deaths from measles are common in some European countries, and this is directly related to poor vaccine coverage (see 1). Measles has almost been eliminated in Britain, but high levels of population immunity (>90%) are needed to prevent the recurrence of epidemics. There are already warning signs—outbreaks of measles have recently been reported in Steiner schools in Yorkshire, Gloucestershire, and Hampshire, where children are not vaccinated for philosophical reasons. Transmission of measles among such pockets of unvaccinated children has the potential to cause outbreaks in the general population.



Coverage of measles vaccine and deaths from measles (data from

WHO)

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It would seem that MMR vaccine has become the victim of its own success. When disease elimination is close, attention inevitably shifts to the side effects of the vaccine. The latest findings from the Health Education Authority, which has been tracking a random sample of mothers with children aged 0-2 years since 1991, found that 8% of mothers now consider that the MMR vaccine presents a greater risk than the diseases it protects against and that 20% consider the vaccine to have a moderate or high risk of side effects. Mothers in social categories ABC1 were less confident about MMR safety and potential risks than their C2DE counterparts.

Perception of the severity of disease has also changed substantially. Since 1991 there has been a 7% drop among mothers who would strongly agree to have any future child immunised. Of these, 33% believe MMR presents substantial risks to their child, including brain damage, a rise of 7% since February 1997. In October 1994, just before the national immunisation campaign against measles and rubella, 55% of mothers considered measles to be a very serious illness; now only 20% do so. We should learn from the experience of pertussis, where a sustained, misinformed media campaign against the vaccine throughout the 1970s saw vaccine coverage drop from 81% to 31%. Pertussis immunisation was disrupted in many other countries by anti-vaccination movements, and these countries experienced a disease incidence up to 100 times greater than in countries where high coverage was maintained (*Lancet* 1998;351:356-61).

We are fortunate in Britain in having strong surveillance systems that are able to rapidly detects changes in vaccine coverage and disease incidence. We cannot, however, afford to let our guard drop. Now that the issue of MMR vaccine safety has been resolved in the scientific press, it is important to restore public confidence in the vaccine.

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- Nicoll, A., Elliman, D., Ross, E. (1998). MMR vaccination and autism 1998. *BMJ* 316: 715-716 [Full text]
- Miller, E., Waight, P., Pebody, R G, Paunio, M, Ruutu, P, Lawrenson, R., Farmer, R. (1998). Measles, measles vaccination, and Crohn's disease. *BMJ* 316: 1745-1745 [Full text]

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principal mechanisms—first, by causing damage to DNA and, second, by inducing immunological unresponsiveness. In mice tumour necrosis factor-α polymorphism determines the ability of acute low-dose ultraviolet B radiation to affect cutaneous immunity adversely.[13] The ability to predict an individual patient's genetic and environmental susceptibility to cancer and acute rejection will enable clinical management to be tailored to optimise graft survival and minimise patient morbidity.

In the shorter term prophylactic therapy with synthetic retinoids is likely to be used more liberally than now. There is good evidence that these agents can prevent skin cancer in kidney recipients, albeit with side-effects such as dry mouth and hair loss.[14]

For now, high-risk patients need to be persuaded to treat sunshine as radiation. The level of awareness of risk is disappointing. Despite verbal advice and written information at time of hospital discharge for all newly transplanted patients at St James's Hospital, Leeds, only half of them subsequently recall receiving advice, and compliance with sun protection measures is poor.[15]

Finally, in weighing up risk and benefit for the patient, it is important to remember that many studies have shown that renal-transplant patients have a better quality of life and live longer than do patients maintained on dialysis.[16] Also the patient's view of the balance of risks has to be taken into account; it may differ from that of the medical adviser.[17]

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1 Hiesse C, Rieu P, Kriaa F, et al. Malignancy after renal transplantation: analysis of incidence and risk factors in 1700 patients followed during a 25-year period. *Transplant Proc* 1997; 29: 831-33.

2 Hoshida Y, Tsukuma H, Yasunaga Y, et al. Cancer risk after renal transplantation in Japan. *Int J Cancer* 1997; 71: 517-20.

3 Al-Sulaiman MH, Al-Khader AA. Kaposi's sarcoma in renal transplant recipients. *Transplant Sci* 1994; 4: 46-60.

4 Opelz G, Schwarz V, Grayson H, et al. Multicenter analysis of posttransplant malignancies. In: Touraine JL, et al, eds. Cancer in transplantation; prevention and treatment. Dordrecht: Kluwer, 1996; 17-23.

5 Bouwes Bavinck JN, Hardie DR, Green A, et al. The risk of skin cancer in renal transplant recipients in Queensland, Australia. *Transplantation* 1996; 61: 715-21.

6 Hartevelt MM, Bouwes-Bavinck JN, Kootte AM, et al. Incidence of skin cancer after renal transplantation in the Netherlands. *Transplantation* 1990; 49: 506-09.

7 London NJ, Farmery SM, Will EJ, et al. Risk of neoplasia in transplant patients. *Lancet* 1995; 346: 403-06.

8 Montagnino G, Lorca E, Tarantino A, et al. Cancer incidence in 854 kidney transplant recipients from a single institution: comparison with normal population and with patients under dialytic treatment. *Clin Transplantation* 1996; 10: 461-69.

9 Ko CB, Walton S, Keczkes K, Bury HP. The emerging epidemic of skin cancer. *Br J Dermatol* 1994; 130: 269-72.

10 Birkeland SA, Storm HH, Lamm LU, et al. Cancer risk after renal transplantation in the Nordic countries, 1964-1986. *Int J Cancer* 1995; 60: 183-89.

11 Allen RDM, Chapman JR. Long term complications: neoplasia. In: Allen and Chapman, eds. A manual of renal transplantation. London: Edward Arnold: 1994, 241-45.

12 Boyle J, MacKie RM, Briggs JD, et al. Cancer, warts, and sunshine in renal transplant patients: case-control study. *Lancet* 1984; i: 702-05.

13 Vincek V, Kurimoto I, Medema JP, Prieto E, Streilein JW. Tumour necrosis factor α polymorphism correlates with deleterious effects of ultraviolet B light on cutaneous immunity. *Cancer Res* 1993; 53: 728-32.

14 Bouwes Bavinck JN, Tieben LM, Van Der Woude FJ, et al. Prevention of skin cancer and reduction of keratotic skin lesions during acitretin therapy in renal transplant recipients: a double-blind, placebo-controlled study. *J Clin Oncol* 1995; 13: 1933-38.

15 Seukeran DC, Newstead CG, Cunliffe WJ. The compliance of renal transplant recipients with advice about sun protection measures. *Br J Dermatol* (in press).

16 Laupacis A, Keown P, Pus N, et al. A study of the quality of life and cost-utility of renal transplantation. *Kidney Int* 1996; 50: 235-42.

17 Holley JL, McCauley C, Doherty B, Stackiewicz L, Johnson JP. Patients' views in the choice of renal transplant. *Kidney Int* 1996; 49: 494-98.

Vaccine adverse events: causal or coincidental?

See pages 637, 646

Although immunisations rank among the most important public-health measures, no vaccine is perfectly safe.[1,2] Because vaccines are given to millions of healthy people, usually infants, extremely high standards for vaccine safety are demanded.[3] It is therefore important to examine, critically and with an open mind, the report by Andrew Wakefield and colleagues of several children whose chronic bowel and behavioural abnormalities were linked by their parents and physicians to measles, mumps, and rubella (MMR) vaccination.

An adverse event can be said to be caused by a vaccine (ie, a true reaction) if it is associated with a specific laboratory finding[4] and a specific clinical syndrome[5] or both. Alternatively, a clinical or epidemiological study is needed to find out whether the rate of a given syndrome in vaccinated individuals exceeds that expected among unvaccinated controls. Such studies require acquisition of data in an unbiased way.[3] Because of the inherent methodological limitations of epidemiological studies, biological plausibility, consistency, strength, and specificity of association must also be considered in inferring causation.[1,2] How well then do the features of the association reported by Wakefield and colleagues fit with causality?

First, hundreds of millions of people worldwide (including those in Scandinavia and North America, where there are excellent clinical facilities) have received measles-containing vaccine without developing either chronic bowel or behavioural problems since the mid-1960s. This finding provides important negative evidence as well as an appropriate framework for the assessment of the cases described by Wakefield and colleagues—namely,

Maximum and current reported cases of vaccine-preventable diseases and adverse events, USA

Disease	Prevaccine era* (year)	1997†	% change
Diphtheria	206 939 (1921)	5	−99·99
Measles	894 134 (1941)	135	−99·98
Mumps	152 209 (1968)	612	−99·60
Pertussis	265 269 (1934)	5519	−97·92
Polio (wild)	21 269 (1952)	0	−100·00
Rubella	57 686 (1969)	161	−99·72
Congenital rubella syndrome	20 000 (1964–5)†	4	−99·98
Tetanus	1560 (1948)†	43	−97·24
Invasive Hib disease	20 000 (1984)†	165	−99·18
Total	1639 068†	6644	−99·59
Vaccine adverse events	0	11 365	+++

*Maximum cases reported in prevaccine era and year.
†Provisional. †Estimated because no national reporting existed in the prevaccine era.
Hib = *Haemophilus influenzae* b

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that if MMR vaccine does causes this syndrome, it does so extremely rarely.

Is the syndrome reported today clinically unique? Ileal lymphoid hyperplasia is non-specific. Autism was known well before MMR vaccine became available. Are there unique laboratory features, including detection of vaccine viruses in clinical specimens where they would not be expected? Although Wakefield has reported the detection of these viruses in patients with inflammatory bowel disease (IBD), other investigators, using more sensitive and specific assays, have not been able to reproduce these findings.[6,7] Another negative report, by M A Azfal and colleagues, is published in today's *Lancet*. There is no report of detection of vaccine viruses in the bowel, brain, or any other tissue of the patients in Wakefield's series.

This leaves epidemiology as the other means of evaluating causation. Is there selection bias? The Wakefield report is based on cases referred to a group known to be specially interested in studying the relation of MMR vaccine with IBD, rather than a population-based study. A first dose of MMR vaccine is given to about 600 000 children every year in the UK, most during the second year of life, the time when autism first becomes manifest. Not surpritingly, therefore, some cases will follow MMR vaccination. Biased case-ascertainment, as in this study, will exaggerate the association.

Was there recall bias? It is usually difficult to date precisely the onset of a syndrome such as autism. Parents and others may attempt to relate its onset to an unusual event such as coincidental postvaccinal reaction. The clearest example of such an association was the link betweeen infantile spasms and pertussis vaccines; the vaccine tends to unmask rather than cause the syndrome.[1]

There are other reasons for doubt about the association reported by Wakefield and colleagues. They suggest that MMR immunisation may lead to IBD, which results in malabsorption, consequent neurological damage, and "autism". However, behavioural changes preceded bowel symptoms in almost all their reported cases. No clear case-definition was presented, a necessary requirement of a true new clinical syndrome and an essential step in any further research. Recent evidence also suggests that measles (or MMR) does not contribute to the development of IBD,[8] the antecedent necessary for autism according to Wakefield and colleagues. Moreover, they have not completed the critical virological studies in these children needed to support their hypothesis that persistent measles (vaccine) viral infection plays a part in the causation of the illness.

Vaccine-safety concerns gain prominence whenever the incidence of vaccine-preventable diseases falls to negligible levels and when the number of vaccine adverse events, whether true reactions or those coincidental to the vaccination but falsely attributed to it (table), rises as a consequence of high vaccine coverage.[9] False attribution usually occurs because many developmental abnormalities first manifest in the early years of life, which is also when several vaccines—which can cause crying, fever, and, occasionally, febrile seizures—are given.

Effective and credible systems are needed for the detection of vaccine-associated adverse events through pharmacovigilance, for distinguishing causal reactions from coincidental reactions by pharmacoepidemiological or other studies, and for risk communication.[1-3,9] Without such a system, vaccine-safety concerns such as that reported by Wakefield and colleagues may snowball into societal tragedies when the media and the public confuse association with causality and shun immunisation. This painful history was shared by the UK (among others) over pertussis in the 1970s[10] after another similar case- series was widely publicised,[11] and it is likely to be repeated all too easily over MMR.[12] This would be tragic because passion would then conquer reason and the facts again in the UK.

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1 Howson CP, Howe CJ, Fineberg HV, eds. Institute of Medicine. Adverse effects of pertussis and rubella vaccines: a report of the Committee to Review the Adverse Consequences of Pertussis and Rubella Vaccines. Washington, DC: National Academy Press, 1991.
2 Stratton KR, Howe CJ, Johnston RB, eds. Adverse events associated with childhood vaccines: evidence bearing on causality. Washington DC: National Academy Press, 1994.
3 Chen RT. Special methodological issues in pharmacoepidemiology studies of vaccine safety. In: Strom BL, ed. Pharmacoepidemiology. Chichester: John Wiley, 1994: 581–94.
4 Forsey T, Bentley ML, Minor PD, Begg N. Mumps vaccines and meningitis. *Lancet* 1992; 340: 980.
5 Kilroy AW, Schaffner W, Fleet WF Jr, et al. Two syndromes following rubella immunization: clinical observations and epidemiological studies. *JAMA* 1970; 214: 2287–92.
6 Iizuka M, Nakagomi O, Chiba M, et al. Absence of measles virus in Crohn's disease. *Lancet* 1995; 345: 199.
7 Haga Y, Funakoshi O, Kuroe K, et al. Absence of measles viral genomic sequence in intestinal tissues from Crohn's disease by nested polymerase chain reaction. *Gut* 1996; 38: 211–15.
8 Metcalf J. Is measles an infection associated with Crohn's disease? *BMJ* 1998; 316: 166.
9 Chen RT, Rastogi SC, Mullen JR, et al. The Vaccine Adverse Event Reporting System (VAERS). *Vaccine* 1994; 12: 542–50.
10 Gangarosa EJ, Galazka AM, Wolfe CR, et al. Impact of the anti-vaccine movements on pertussis control: the untold story. *Lancet* 1998; 351: 356–61.
11 Kulenkampff M, Schwartzman JS, Wilson J. Neurological complications of pertussis inoculation. *Arch Dis Child* 1974; 49: 46–49.
12 Begg N, Ramsay M, White J, Bozoky Z. Media dents confidence in MMR vaccine. *BMJ* 1998; 316: 561.

How the colon begets gallstones

Bile is secreted by the liver, and gallstones are generally formed in the gallbladder. How then can the intestine influence the biliary system? Interest in this question has recently revived, especially with reference to the formation of cholesterol gallstones.

In normal human bile the three bile salts that predominate are the conjugates of cholate, of chenodeoxycholate, and of deoxycholate. Cholate and chenodeoxycholate, the primary bile salts, are synthesised by the liver from cholesterol. Deoxycholate is entirely the product of colonic bacterial metabolism of any cholate that has escaped reabsorption by the active bile-salt transport system in the ileum (figure). Some of the newly formed deoxycholate is reabsorbed through the colon and returned to the liver via the portal system. After hepatic conjugation, deoxycholate joins the major enterohepatic circulation of bile salts, being subsequently recirculated mainly by ileal absorption. Deoxycholate constitutes 10–30% of the bile-salt pool. What effect does the extent of enterohepatic circulation of this bacterial metabolite have on bile lithogenicity?

Cholesterol gallstones form in bile that contains more cholesterol than can be maintained in micellar or vesicular solution by its solubilisers, bile salt and phospholipid. Oral administration of chenodeoxycholate has long

Original research Welcome paulkim

Research letters [illegible] Volume 351, Number 9103 [illegible]

Previous ‹ › Next

Absence of measles-virus genome in inflammatory bowel disease

M A Afzal, P D Minor, J Begley, M L Bentley, E Armitage, S Ghosh, A Ferguson

See Commentary

It has been suggested that inflammatory bowel disease is associated with measles virus and measles vaccination.[1-3] The presence of measles virus in Crohn's and ulcerative colitis tissues has been described.[4-5] We used a sensitive molecular approach to examine the presence or absence of measles virus genome in clinical specimens from 19 patients with inflammatory bowel disease and 11 controls.

We established a highly sensitive RT-PCR-nested PCR system by combining the EZ rTth RNA PCR and AmpliTaq (Perkin Elmer) technologies and measles N-gene specific primers. This combination in our hands consistently amplified measles virus-specific sequences from virus-infected tissue culture fluid down to $5{\cdot}5\times10^{-2}$ to $5{\cdot}5\times10^{-3}$ plaque forming unit/reaction. The assay is therefore nearly 1000-10000 fold more sensitive than assays for infectious virus. We further improved the system by assaying the nested PCR products with the digoxigenin antibody and Southern blots which provided a clear endpoint. With this system we have so far examined 93 colonoscopic biopsy specimens (of ulcerated and of apparently normal colonic mucosa) and 31 peripheral blood lymphocyte preparations, from nine patients with Crohn's disease, nine with ulcerative colitis, one with indeterminate colitis, and 11 controls with non-inflammatory conditions. All patients gave informed consent and study was approved by the local ethical committee. Five of the 30 patients had a history of measles vaccination (confirmed by their general practitioner). All 30 had serum neutralisation antibodies against measles virus, and have therefore been exposed at some time either to wild-type or to vaccine measles viruses. Positive control samples used in each assay run were a wild-type measles virus grown in tissue culture, and brain material of a patient who died with subacute sclerosing panencephalitis (SSPE).

No measles-specific DNA fragments have been detected in the nested PCR products generated from the blood lymphocytes or colonoscopic biopsy specimens of these 30 patients. All positive controls produced measles-specific DNA products of the correct size and had distinct nucleotide sequences. We also checked the validity of the RT-PCR-nested PCR system by spiking measles virus into the clinical materials and found no difference in terms of positivity. This suggests that substances which may degrade measles RNA molecules or inhibit RT-PCR activity were not present or active in the clinical tissues examined. Based on the amount of human beta actin gene DNA detected in internal controls, each biopsy specimen contains 1 million cells, therefore, compared with other techniques,[4-5] probably more cells were examined by RT-PCR methods for the presence of measles virus genome.

Two further points illustrate the extreme caution with which studies of this type must be interpreted. Some non-specific bands were present in the N-gene nested PCR products of the clinical material. These were significantly larger than the target fragment and became visible only in digoxigenin antibody assays. They did not react with a measles-specific probe in Southern blots and could not be sequenced with measles N gene primers. We also had one incident of cross-contamination. Material from one biopsy sample gave a positive result which we traced back to cross-contamination from the positive control at the primary PCR level. This has been confirmed by nucleotide sequencing of the fragment, which had an identical sequence to that of the positive control. Other specimens from this patient--two colonic biopsies, one lymphocyte preparation, and one serum sample--were negative by RT-PCR-nested PCR.

We believe that the system established at NIBSC is sufficiently sensitive to identify measles virus genome, if it existed, in the clinical material examined. Our experience also demonstrates that even with the most scrupulous attention to methodology and laboratory procedures, cross-contamination of specimens can occasionally occur; and also that considerable experience and a range of methodologies may be needed to recognise non-specific reactions which might be interpreted as positive if confirmatory techniques are not applied. We concluded that with the best available RT-PCR-nested PC technology, measles virus genome is not present in gut mucosal biopsies from patients with Crohn's disease or ulcerative colitis.

1 Ekbom A, Wakefield AJ, Zack M, Adami HO. Potential measles infection and subsequent Crohn's disease. *Lancet* 1994; **344:** 508-10 [PubMed].

2 Ekbom A, Daszak P, Kraaz W, Wakefield AJ. Crohn's disesase after in-utero measles virus exposure. *Lancet* 1996; **348:** 515-17 [PubMed].

3 Thompson NP, Montgomery SM, Pounder RE, Wakefield AJ. Is measles vaccination a risk factor for inflammatory bowel disease? *Lancet* 1995; **345:** 1071-74 [PubMed].

4 Wakefield AJ, Pittilo RM, Sim R, et al. Evidence of persistent measles virus infection in Crohn's disease. *J Med Virol* 1993; **39:** 345-53 [PubMed].

5 Wakefield AJ, Sim R, Akbar AN, Pounder RE, Dhillon AP. In situ immune response in Crohn's disease: a comparison with acute and persistent measles virus infection. *J Med Virol* 1997; **51:** 90-100 [PubMed].

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Previous ‹ › Next

BMJ

MMR vaccination and autism 1998

Déjà vu—pertussis and brain damage 1974?

News p 724

The media excitement and public concern after a *Lancet* report linking measles, mumps, and rubella (MMR) vaccine with autism[1] kindles a sense of déjà vu. It is highly reminiscent of similar scares over pertussis in the 1970s,[2] which resulted in much suffering and many deaths from pertussis both in Britain and internationally.[2 3]

Britain's vaccination programme has hugely reduced the incidence of diphtheria, haemophilus meningitis, measles, polio, pertussis, congenital rubella, and tetanus.[4] As the incidence of these diseases has fallen vaccine safety has assumed greater importance, especially in parents' minds. Any safety issue requires cool scientific consideration.[5] Here the hypothesis is that MMR leads to a non-specific gut condition permitting the absorption of non-permeable peptides, which in turn cause serious developmental disorders.[1] Supportive evidence consists of cases referred to a gastroenterology group. The data published comprises 11 boys and one girl, each with bowel abnormalities and serious developmental regression (nine had autism). In eight children parents reported regression starting shortly after the children received MMR.[1]

An editorial accompanying the article and a recent review by the World Health Organisation list the considerable evidence against this and previous related theories from the same group.[1 5] Since each year over 600 000 British children receive MMR in their second year, an age when autism can typically manifest itself, chance alone dictates that some cases will appear shortly after vaccination.[5] Cases will be selectively referred to a group known for its interest in MMR, inflammatory bowel disease, and autism, so the hypothesis rests on clinical anecdote rather than an epidemiologically sound base.

Proved serious vaccine reactions are characterised by specific clinical or laboratory findings, but the non-specific nature of the developmental and gut abnormalities in these cases is striking, and no precise case definition is offered.[1] No vaccine viruses were reported in the children's biological specimens, though the researchers have previously reported viruses in bowel tissues of children with inflammatory bowel disease, findings which others have been unable to confirm.[7]

Epidemiological evidence is unsupportive: the WHO found no links between measles, MMR, and inflammatory bowel disease[5]; and a survey of conditions associated with autism did not mention inflammatory bowel disease.[6] National data seem to indicate a rise in the incidence of autism, but it started over a decade before MMR's introduction in 1988 and showed no change at that time (M Bax, D Lawton, Family Fund Trust, unpublished data). This evidence suggests either no causative association or one that is exceedingly rare. These and many other data relating to MMR safety have been reviewed by the Joint Committee on Vaccination and Immunisation, which found no case for changing vaccination policy. Unproved theories are no basis for dropping a vaccine of proved global safety and effectiveness.[1 5]

Despite the lack of evidence of a causal relation, and the experience of other hypotheses from the same group (linking first wild measles, then measles vaccine, and latterly MMR with bowel disease) not standing up to independent scrutiny[5 7] much parental anxiety has resulted. MMR immunisation rates have begun to decline and those at the "sharp end" of immunisation—general practitioners, health visitors, and community paediatricians—are experiencing parental inquiries.[8] Any decline in immunisation, or the giving of MMR as three injections at annual intervals (as suggested by one of the report's authors), will undo the recent near elimination of measles and rubella in the UK.[8]

The experience with pertussis in the 1970s was also based on anecdotal case reports linking pertussis vaccination with infant brain damage.[9] Again a temporal link between a vaccine and a devastating childhood condition whose natural peak onset was at the very time when most children received that vaccine was misinterpreted as a causal relation. A national study eventually showed that, while there was a temporal association with encephalopathy, any risk of lasting damage was so rare as to be unquantifiable.[10] But the initial report, then as now, attracted media attention; parental and professional anxiety soared; and national immunisation rates fell from 80% to 30%. The number of susceptible children rose, and in the 12 years after 1976 three major pertussis epidemics accounted nationally for over 300 000 notifications and at least 70 deaths. The suffering of families experiencing long miserable illnesses was considerable, and in some cases long term damage ensued. Some parents came to believe that an immunisation they had approved had damaged their child.

There are differences between then and now. The connection of encephalopathy with pertussis vaccine was biologically more plausible than the link proposed for MMR and autism. The original national study[10] has already shown no link between measles vaccine and long term developmental disorders.[11] Detection of vac-

BMJ 1998;316:715-6

cine reactions is more efficient, with international data sharing and a careful eye on safety by independent scientific experts on the Joint Committee on Vaccination and Immunisation and committees of the Medicines Control Agency. Surveillance results in product withdrawal when there is clear evidence of a safety issue.

In the 1970s immunisation had a low priority, and evidence based information for those doing the immunising was minimal. District immunisation coordinators did not exist, and vaccination rates slumped partially because it was unclear whose responsibility it was to do anything about them.[12] The pertussis experience must not be repeated with MMR vaccine. While vaccine can be guaranteed to be without any risk, this has to be weighed against the huge advantages of protection against disease. Seeds of concern have been sown among parents and no doubt will continue to be spread. Those advising families must make sure parents can base their decisions on hard science and evidence.

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1 Wakefield AJ, Murch SH, Linnell AAJ, Casson DM, Malik M, Berelowitz M, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis and pervasive developmental disorder in children. *Lancet* 1998;351:637-41.
2 Gangarosa EJ, Galazka AM, Wolfe CR, Phillips LM, Gangarosa RE, Miller E, et al. Impact of the anti-vaccine movements on pertussis control: the untold story. *Lancet* 1998;351:356-61.
3 Chen RT, Destefano F. Vaccine adverse events: causal or coincidental? *Lancet* 1998;351:611-2.
4 Salisbury DM, Begg NT, eds. *Immunisation against infectious disease.* London: HMSO, 1996.
5 World Health Organisation. Expanded programme on immunization (EPI)—association between measles infection and the occurrence of chronic inflammatory bowel disease. *Wkly Epidemiol Rec* 1998;73:33-40.
6 Fombonne E, Du Mazaubrun C, Cans C, Grandjean H. Autism and associated medical disorders in a French epidemiological survey. *Am Acad Child Adolesc Psychiatry* 1997;36:1561-9.
7 Metcalfe J. Is measles infection associated with Crohn's disease? *BMJ* 1998;316:166.
8 Begg N, Ramsay M, White J, Bozoky Z. Media dents confidence in MMR vaccine. *BMJ* 1998;316:561.
9 Kulenkampff M, Schwartzman JS, Wilson J. Neurological complications of pertussis inoculation. *Arch Dis Child* 1974;49:46-9.
10 Miller D, Madge N, Diamond J, Wadsworth J, Ross E. Pertussis immunisation and serious acute neurological illnesses in children. *BMJ* 1993;307:1171-6.
11 Miller D, Wadsworth J, Diamond J, Ross E. Measles vaccination and neurological events. *Lancet* 1997;349:730-1.
12 Nicoll A, Elliman D, Begg NT. Immunisation: causes of failure and strategies and tactics for success. *BMJ* 1989;299:808-12.

Hydroxychloroquine retinopathy: is screening necessary?

Intensive screening is not necessary at normal doses

The 4-aminoquinolines (chloroquine and hydroxychloroquine) are used as second line agents for their disease modifying effect in rheumatoid arthritis and systemic lupus erythematosus. The association between chloroquine therapy and pigmentary maculopathy has been known since 1959.[1] The manufacturer's datasheet suggests that all patients receiving hydroxychloroquine should undergo an ophthalmic examination, including a central visual field test, at least twice a year. If implemented this recommendation would have a noticeable impact on the ophthalmic service. Is it necessary?

The earliest sign of chloroquine retinopathy is a paracentral scotoma. This so called premaculopathy can be detected with an Amsler chart.[2] Later, subtle pigmentary mottling develops at the macula, and this may progress to the characteristic bull's eye maculopathy and widespread retinal pigment epithelial atrophy. In its early stages chloroquine retinopathy is reversible by stopping the drug.[3] Hydroxychloroquine given at currently prescribed doses is thought to be less toxic than chloroquine.

The recommended dose for hydroxychloroquine is 6.5 mg/kg lean body weight per day.[4] In their prospective study of 73 patients treated with hydroxychloroquine for at least 18 months, Morsman et al reported one case of possible toxic retinopathy—and this patient had received twice the recommended daily dose.[5] In a retrospective study of 82 patients taking hydroxychloroquine for over a year (mean 38.6 months) Spalton et al found no cases of retinopathy.[6] No correlation was present between the computerised visual field indices and any measure of increasing drug exposure. The authors concluded that visual field testing was unnecessary in these patients.[6] Bernstein analysed all published cases and Food and Drug Administration reports of hydroxychloroquine retinopathy. He found no evidence of permanent visual loss among more than 1500 patients who did not exceed the recommended daily dosage for up to 10 years.[7] More recently, however, two well documented cases of hydroxychloroquine retinopathy have been reported in patients treated for 6.5 and 8 years without exceeding the recommended maximum daily dose.[8]

The Royal College of Ophthalmologists' guidelines for managing patients receiving hydroxychloroquine recommend a baseline ophthalmic examination at the start of treatment, including best corrected visual acuity, fundoscopy, and a central visual field test.[9] Thereafter the prescribing medical practitioner should be responsible for any screening considered necessary. Patients should be warned to report any visual disturbance and may be given an Amsler chart to use on a monthly basis. No further ophthalmic examination is necessary unless the patient becomes symptomatic.

BMJ 1998;316:716-7

CORRESPONDENCE

Autism, inflammatory bowel disease, and MMR vaccine

Sir—We are concerned about the potential loss of confidence in the mumps, measles, and rubella (MMR) vaccine after publication of Andrew Wakefield and colleagues' report (Feb 28, p 637),[1] in which these workers postulate adverse effects of measles-containing vaccines. As a result, we fear there may be a reduction in vaccine uptake in the UK and elsewhere. The main thrust of the report is to add to the record 12 possible cases of bowel disease associated with developmental regression (including autism), which is a useful contribution to research. However, an association was also alluded to between these two factors and environmental triggers such as receipt of MMR vaccine.

Wakefield and co-workers state "We did not prove an association between measles, mumps, and rubella vaccines and the syndrome described". However, there are enough references in the text to lead the reader to the assumption that there is sufficient evidence provided by the study, and by other scientific publications, to suggest that there is a likely (although as yet unproven) link.

The study suggests a temporal relation between the so-called autism-bowel syndrome and administration of MMR in eight of the 12 cases. However, the interval between receipt of vaccine and onset of symptoms is provided in only five cases (1–14 days), and the age at which the vaccine was given was provided in only three (15 months, 16 months, and 4·5 years). Parents identified MMR to be the immediate precursor of developmental delay in eight of the 12 children, but developmental delay is likely to be detected by a gradual awareness over a period of time, not on a particular day. Although autism is rarely diagnosed before 18 months, the insidious onset of symptoms often predates the diagnosis by many months. As described by Wakefield, parents had trouble making a temporal link between the onset of autism and the onset of gastrointestinal symptoms for similar reasons. We therefore question the conclusion that there was a temporal association of the autism-bowel syndrome and MMR.

To prove a causal relation is much harder—it requires a selection of patients and matched controls, and a sample size that is capable of detecting a statistically significant difference between the two groups. The investigators may need to be blinded for such aspects as clinical assessments and laboratory tests. How does Wakefield's study match up? There was no patient selection other than 12 patients referred to him. There were no controls. There was no blinding of investigators. The accompanying commentary by Robert Chen and Frank DeStefano[2] elegantly explains the difference between temporal and causal association. We concur with them that Wakefield's study fails at every level to make a causal association.

Is it possible that we are confronted by a genuine causal association which has shown up by chance in these eight cases? Is it possible that these cases have brought to light a previously unnoticed association? Wakefield claims that the association between autism and MMR has been documented in the past—an important point to clarify. However, the two references they cite from Fundenburg and Gupta (refs 16 and 17 in their report) need further scrutiny. The first deals mainly with the association of autism and transfer factor (DLyE) and also mentions "live rubella immunization at 15 months has precipitated fever convulsions followed by autistic symptoms; so has live hepatitis B vaccine in 2 infants at 2 years". These anecdotal associations do not advance the argument for causality. We could not obtain the Gupta reference through usual library channels.

Wakefield and colleagues' findings confront us with a new hypothesis—that measles-containing vaccine may trigger developmental regression. It is known that such speculation may seriously damage important public health programmes, causing a decline in vaccine uptake and a rise in the target disease.[3] We can now expect such damage to occur in many countries. We question the merit of publishing this particular study.

Publication of this study is especially tragic because WHO and all consulted national public health authorities agree that it does not alter in any way the continued recommendation to use measles-containing vaccines throughout the world. Current measles containing vaccines are highly safe and effective.

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1 Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998; 351: 637–41.
2 Chen RT, DeStephano F. Vaccine adverse events: causal or coincidental? *Lancet* 1998; 351: 611–12.
3 Gangarosa EJ, Galazka AM, Wolfe CR, et al. Impact of anti-vaccine movements on pertussis control: the untold story. *Lancet* 1998; 351: 356–61.

Sir—Andrew Wakefield and colleagues'[1] report a case series of 12 patients and use this to generate a hypothesis that gastrointestinal disease and an associated developmental disorder may be related to MMR. This research was widely reported in the mass media and has generated considerable public concern, despite the weight of evidence supporting the efficacy and safety of MMR vaccination discussed by Robert Chen and Frank DeStefano.[2] Previous experience suggests that adverse publicity about vaccination, even though subsequently shown to be exaggerated or unfounded, results in reduced vaccine coverage with serious public health consequences.[3] The widespread reporting of this case series is likely to have a similar impact.

The publicity generated by this paper is out of proportion to the strength of evidence presented. Description of the strength of research evidence is straightforward. There are standard scoring systems in common use that enable consumers of research to quickly understand the weight that should be given to the evidence presented.[4] In this example a reasonable score might be IV—"evidence inadequate owing to problems of methodology, eg, sample size, length or comprehensiveness of follow up, or conflict of evidence".[5] This paper was marked Early Report and accompanied by a critical commentary,[2] although the report itself did not contain a strength of evidence score.

Research is essential to the advancement of knowledge and will always be newsworthy. However, we believe that it is now time for research publications to carry health warnings so that the public and health professionals are adequately appraised about the strength and quality of evidence presented. A critical commentary published along side is helpful, but not sufficient.

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1 Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998; 351: 637–41.
2 Chen RT, DeStefano F. Vaccine adverse events: causal or coincidental? *Lancet* 1998; 351: 611–12.
3 CDSC. MMR vaccine coverage falls after adverse publicity. *Commun Dis Rep CDR Wkly* 1998; 8: 41, 44.
4 Stevens A, Raftery J, eds. Health care needs assessment: the epidemiologically based needs assessment reviews. Oxford: Radcliffe, 1997.
5 Williams MH, Frankel SJ, Nanchahal K, et al. Total hip replacement. In: Health care needs assessment: the epidemiologically based needs assessment reviews, vol 1. Oxford: Radcliffe Medical Press, 1994.

Sir—By publishing Andrew Wakefield and colleagues'[1] work purporting to show a link between MMR vaccination and inflammatory bowel disease and autism and related problems you give increased credence to their report. *The Lancet* is a prestigious, peer reviewed journal with high public profile. The profession, journalists, the public, and especially distressed parents of ill children suppose that a publication in your journal will be true. In this example you print a commentary, which if it had been a peer reviewer's report, should have led to the rejection of the paper.

The result of publication and the subsequent general publicity is predictable, from previous experience well documented by E J Gangerosa et al (Jan 31, p 356)[3] for whooping cough vaccine. Such publicity has led to parents refusing vaccination for their children and a resurgence of the disease (and deaths), and more anguish for the parents who expected recompense from the courts which usually failed for lack of evidence of causality. Also it frightened many manufacturers from continuing development and production of vaccines.

If my predictions are correct, then I think you will bear a heavy responsibility for acting against the public health interest which you usually aim to promote. Moreover, you will only increase the anguish of the parents of the sick children with whom all doctors will sympathise.

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1 Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998; 351: 637–41.
2 Chen RT, DeStephano F. Vaccine adverse events: causal or coincidental? *Lancet* 1998; 351: 611–12.
3 Gangarosa EJ, Galazka AM, Wolfe CR, et al. Impact of anti-vaccine movements on pertussis control: the untold story. *Lancet* 1998; 351: 356–61.

Sir—Renewed speculation surrounding the safety of MMR vaccine has followed the publication of Andrew Wakefield and colleagues'[1] report of parents or physicians linking MMR vaccine with the development of autism. The Inflammatory Bowel Disease Study Group (IBDSG) has previously suggested links between exposure to wild measles virus and/or vaccine-related strains and an increased risk of developing Crohn's disease and ulcerative colitis. Evidence published in peer-reviewed journals has, however, failed to confirm a relation between measles vaccination and subsequent development of inflammatory bowel disease.[2] The epidemiological flaws in this latest paper concerning autism have also been well rehearsed.[3]

There is already evidence that current speculation has undermined confidence in the vaccine since coverage of MMR vaccine fell by 1% between the second and third quarters of 1997 across the UK. MMR coverage in Scotland has fallen to 93·7%. An increasing number of parents, according to the latest Health Education Authority tracking programme, now apparently believe that MMR vaccine poses a greater risk than wild measles virus infection.[4] The extent to which this misplaced anxiety is reinforced by professional uncertainty, indecision, and reluctance to promote vaccination has yet to be established, although we have good evidence that this was an important factor in the low uptake of measles vaccination in the 1980s.[5]

There is a temptation to blame the media for the drop in vaccine coverage. There is, after all, a substantial amount of evidence that contradicts the findings of the IBDSG but which tends not to achieve the same prominence in the popular press. No wonder parents are worried—they tend to hear only one side of the argument. But is it fair to blame the press? Should not the researchers shoulder the burden of responsibility? It is, after all, an awesome responsibility.

It should not be forgotten that measles vaccination has substantially improved the health of children worldwide, protecting against the considerable burden of mortality and morbidity caused when the transmission of wild measles virus went unchecked. In denting parental, and possibly professional, confidence in MMR vaccination, we must not forget the consequences of wild measles virus infection, should we see its resurgence. One in 15 children would develop complications ranging from ear problems and bronchitis to pneumonia and fits. One in 5000 children would develop encephalitis and 15% of them would die. Furthermore, if the IBDSG's earlier theories have any foundation, a resurgence of wild measles virus would itself be a risk factor for the development of inflammatory bowel disease and autism.

The debacle following concerns over the safety and efficacy of pertussis vaccine, based on evidence that was not later substantiated, impeded the control of whooping cough considerably in many European countries. Should we see the same situation with MMR vaccination, it would be another public health disaster.

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1 Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-

specific colitis, and pervasive developmental disorder in children. *Lancet* 1998; 351: 637–41.
2 Metcalf J. Is measles infection associated with Crohn's disease? The current evidence does not prove a causal link. *BMJ* 1998; 316: 166.
3 Chen RT, DeStefano F. Vaccine adverse events: causal or coincidental? *Lancet* 1998; 351: 611–12.
4 Begg N, Ramsey M, White J, Bozoky Z. Media dents confidence in MMR vaccine. *BMJ* 1998; 316: 561.
5 Carter H, Jones IG. Measles immunisation: results of a local programme to increase vaccine uptake. *BMJ* 1985; 290: 1717–19.

Sir—Any future investigation of causation will need to address the two main weaknesses of Andrew Wakefield and colleagues'[1] case series—that the cases were highly selected and the underlying population is not clear. We conducted a population-based study in the summer of 1997 in Swansea which was designed to avoid selection bias and could be replicated across the UK. The study was undertaken in response to concerns being expressed in the local media about the postulated link between MMR and autism; in particular parents had raised the question of whether there could have been a local problem with a batch of faulty MMR vaccine. This aspect of the investigation (particular batches) was unremarkable and not reported here.

The district-wide child health computer system has a vaccination record for all children in Iechyd Morgannwg (formerly West Glamorgan), and it also has information about important medical problems for any children referred to Community Child Health Services. A search was done for all children born since 1990 with an ICD 9 or ICD 10 code for autism.

The computer vaccination history was examined to establish whether the child had received a first-dose MMR vaccination. The proportion of children with autism who had received MMR vaccination was calculated and compared with that for all children in the district.

18 children with a diagnosis of autism, born between 1990 and 1994 were identified, 16 of whom had received MMR vaccination, giving a first-dose MMR vaccination rate for children with autism of 88·9%. The vaccination rate for all children was 95·3%. The difference in vaccination rates is not statistically significant.

The method, based on the rapid interrogation of child-health computer systems could be replicated on a larger scale as a formal, UK-wide, case-control or retrospective cohort study. A case-control study with four controls for every case and an 80% power to detect a two-fold increase in the risk of autism after MMR vaccination would require 691 cases—an assumption of a population MMR coverage of 95%. If the morbidity recording were similar to that of West Glamorgan (population 370 000) this would require combining results from a general population of 14·3 million people. We suggest that this is a practical way of rapidly investigating this speculative association.

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1 Wakefield AJ, Murch S, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998; 351: 637–41.

Sir—We were surprised and concerned that the *Lancet* published the paper by Andrew Wakefield and colleagues[1] in which they alluded to an association between MMR vaccine and a non-specific syndrome, yet provided no sound scientific evidence. The commentary by Robert Chen and Frank DeStefano[2] points out the serious flaws in the paper.

We acknowledge that anecodotal reports may sometimes contribute to the generation of hypotheses, but risk factors for rare conditions, such as those described, can only be identified by well designed epidemiological studies.

This publication provided a platform for the expression of views about MMR vaccination that have no proven scientific foundation: this could have damaging effects on public and professional confidence in vaccines in general. The MMR vaccination programme has been successful in this country, and we are now at a point when the elimination of measles is a real possibility. If, as a result of this paper, parents reject MMR vaccine, this could lead to a re-emergence of measles infection with associated deaths and permanent neurological damage among young children, and a resurgence of rubella infection leading to a rise in congenital rubella births and terminations of pregnancy. Has nothing been learned from the experiences with pertussis vaccine in the 1970s?[3]

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1 Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998; 351: 637–41.
2 Chen RT, DeStefano F. Vaccine adverse events: causal or coincidental? *Lancet* 1998; 351: 611–12.
3 Gangarosa EJ, Galazka AM, Wolfe CR, et al. Impact of anti-vaccine movements on pertussis control: the untold story. *Lancet* 1998; 351: 356–61.

Sir—The account given by Andrew Wakefield and colleagues'[1] is interesting, yet the structure of the study with biased case ascertainment and no suitable controls makes the findings no more than anecdotal. Perhaps the only saving grade for *The Lancet* is the accompanying well balanced commentary.[2]

Chronic non-specific colitis, as described by Wakefield, is a common form of non-infective colonic inflammation in the age group studied. Furthermore, of 329 consecutive colonscopies done at Great Ormond Street Hospital (children aged 1 month to 16 years with chronic diarrhoea), 40 children were noted to have macroscopic ileal/ileocolonic lymphoid nodular hyperplasia, giving a prevalence in this selected population of 12%. 85% of these children had minor immunodeficiencies, as reported by Wakefield, but none had neuropsychiatric disorder.

The investigators concede that they have not proven an association between MMR immunisation and the syndrome described, and have in reality presented no hard data on this matter. The report has led, intentionally or otherwise, to the erroneous assumption by the media and parents of a cause and effect relation between MMR immunisation, inflammatory bowel disease, and developmental disorder, resulting in parental confusion about the safety of immunisation. This country's childhood immunisation programme has dramatically reduced wild-type measles infection with its associated significant morbidity and mortality. Wakefield's account risks setting back child health 30 years through disruption of this programme. If these researchers are able to prove cause and effect between immunisation and the described syndrome they should do so straight away. If they are unable to do so they should publicly set the matter straight lest the health of our nation's children suffers.

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Läkartidningen (Swedish Medical Bulletin) 1998; 11: 1156.

MMR vaccine - connection between autism and intestinal disease

On 28th February 1998 Wakefield et al reported in Lancet on 12 children with intestinal symptoms and regressed development. For 8 of the children a time correlation was seen between debut of symptoms and vaccination against Measles, Mumps and Rubella (MMR vaccine). The authors state that there is no evidence of a connection between the vaccinations and the symptoms. In spite of this statement, the article has drawn much public attention. This is very remarkable since Lancet in the same issue are publishing a comment by Chen and DeStefano, CDC, Atlanta, USA who e.g. note:

Hundreds of millions of children all over the world have received MMR vaccine since the 1970s and 1980s without developing intestinal diseases or behavioural disorder.

It cannot surprise that some cases of autism will accidentally occur in close connection to MMR vaccination since almost all children in e.g. England and Scandinavia are vaccinated at a time where symptoms on autism usually become noticeable.

Several independent studies during recent years have shown no connection between measles and development of chronic intestinal inflammations, which, according to Wakefield, should be prerequisite for the development of autism.

On 8th February 1998 WHO's weekly journal (WERREH) published a thorough review of the information available and actually writes off the suspicions aroused by Wakefield et al. A leader in British Medical Journal of 17th January 1998 declared the hypothesis of a connection between MMR vaccination and inflammatory intestinal disease to be unfounded.

Consequently it is timely to warn that a campaign against vaccination may entail dramatic, and from a public point of view, very sad effects for the vaccination programme. Parents must continue to let their children be vaccinated against measles, mumps and rubella - diseases that are somewhat forgotten but still may cause serious disabilities.

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DEPARTMENT OF HEALTH

From the Chief Medical Officer

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PL/CMO/98/2

Measles, MMR Vaccine, Crohn's disease and Autism

For Information
- All Doctors
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- District Directors of Public Health
- Chief Executives of NHS Trusts
- Medical Directors of NHS Trusts
- Regional Nurse Directors
- Trust Nurse Executive Directors
- Chief Pharmacists of NHS Trusts
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- HA Pharmaceutical Advisors
- Regional Principal Drug Information Pharmacists
- Community Service Pharmacists

27 March 1998

Dear Doctor

Measles, Measles Mumps Rubella (MMR) Vaccine, Crohn's disease and Autism

You will be aware of the continuing media reports and public concern that have arisen over the purported associations between MMR vaccine and Crohn's Disease and autistic spectrum disorders (ASD). Reports of such associations have caused parents considerable anxiety. Some are now refusing to accept MMR vaccine for their children. The purpose of this letter is to provide you with more information that may help in advising parents.

I have taken advice from the Joint Committee on Vaccination and Immunisation, and the Committee on Safety of Medicine and asked the MRC to convene an expert group. This group included experts in virology, epidemiology, immunology, paediatrics, child psychiatry and gastroenterology and met on 23rd March to consider all recent work on measles, measles vaccine, MMR vaccine, Crohn's Disease and ASD. Proponents of the associations were given full opportunity to present their data. Along with published material the MRC expert group was privileged to see as yet unpublished material.

Based on the previous material that I have seen, and on the opinions of experts present at the MRC meeting, I have concluded that there is no link between measles, measles vaccine or MMR immunisation, Crohn's Disease, and ASD. Together with others at the meeting, I was not convinced that any of the studies support suggestions that measles or MMR vaccines are implicated in Crohn's Disease or in autism.

I therefore recommend that children should receive MMR vaccine at the appropriate times, and should not be given the separate component vaccines, since there is no evidence that doing this has any benefit and it may even be harmful. I believe that more research is needed to identify the causes of Crohn's Disease, and ASD, but I do not think that MMR vaccine is in any way implicated in the cause of these conditions.

On measles and MMR the MRC expert group, chaired by Professor Sir John Pattison concluded:

- The available virological and epidemiological evidence does not support a causal role for persistent measles virus infection in Crohn's disease.

- There is no evidence to indicate any link between MMR vaccination and bowel disease or autism.

- There is therefore no reason for a change in the current MMR vaccination policy.

In the remainder of this letter, I will summarise the pieces of research relevant to the above.

Does early measles infection increase the risk of Crohn's Disease?

A case series of four mothers and children from Sweden suggested that children born to women who had suffered from measles at the end of pregnancy might be at higher risk of developing Crohn's Disease in later life (1). Two large studies, one from this country and one from Denmark, with appropriate controls, showed no increased risk of Crohn's Disease (2,3) under these circumstances.

Early exposure to measles virus does not appear to increase the risk of Crohn's Disease.

Measles, MMR Vaccine, Crohn's disease and Autism

PL/CMO/98/2

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27 March 1998

Page 2 of 8

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oes measles vaccination increase the risk of Crohn's Disease?

One study that compared a cohort of children immunised from 1964 with an unimmunised cohort from 1958 suggested an increased risk of Crohn's Disease in the immunised cohort (4). This study was severely criticised on the selection of cases with unmatched controls, differential dropout rates in the two groups, and different means of case ascertainment (5-10). A second study, with Crohn's Disease cases and appropriately matched controls, found no increase in the risk of Crohn's Disease following measles immunisation (11). This finding is confirmed by data from Oxford and from Finland where no increase in Crohn's disease could be linked with the introduction of measles or MMR immunisation. In 1994 around 7 million children in the UK received a combined measles and rubella vaccine. National data from hospital episode statistics show no increase in new cases or exacerbation of existing cases of Crohn's disease following this immunisation campaign. This surveillance will continue.

Measles vaccination does not increase the risk of Crohn's Disease.

Have measles viruses been demonstrated in Crohn's Disease tissues?

Using a variety of different techniques (12,13), the Royal Free Hospital Inflammatory Bowel Disease Study Group (RFH-IBDSG) has suggested that measles virus can be shown to be present in inflammatory bowel tissues affected by Crohn's Disease. Using reagents provided by the RFH-IBDSG, an independent group could not replicate the RFH-IBDSG results (14). Using the most sensitive and specific molecular techniques (reverse transcriptase-polymerase chain reaction (RT-PCR)), three groups of researchers, including the RFH-IBDSG, have not been able to detect measles virus genetic material in either Crohn's Disease affected tissues, normal bowel tissue, or in peripheral blood lymphocytes (15-18).

The demonstrated sensitivity of the RT-PCR methods gives reassurance that if measles viruses were indeed present, they would have been detected. Measles specific antibodies do not appear to be raised in individuals with Crohn's Disease (19,20).

The most sensitive and specific techniques have failed to detect the presence of measles viruses in Crohn's Disease tissues. It remains to be resolved why less sensitive and less specific techniques appear sometimes to give positive results.

Is Autistic Spectrum Disorder (ASD) linked with MMR immunisation?

It has been suggested that the incidence of autism and ASD has increased since the introduction of MMR vaccine, particularly involving a presentation of intellectual deficit in children who were developing normally previously, with onset after MMR vaccination.

The true incidence of autism is uncertain, since the diagnostic criteria have changed over recent years, and children whose conditions were diagnosed as other than autism in the past are now likely to be included within ASD. Autism with developmental regression was well recognised before MMR vaccine became available, and children may present in this way with signs of regression being recognised both before and after receipt of MMR vaccine. The first signs of an autism-like disorder generally appear in the second year of life. This coincides with the time when most children will receive their MMR vaccine. Such coincidence does not imply a causal link.

Since autism has never been linked with measles vaccine, and the only difference between it and MMR vaccine is the addition of rubella and mumps viruses, there is little biological plausibility for these two additional viruses to cause autism, as has been proposed. Similarly, it is difficult to accept that the rubella and mumps components of MMR have caused a bowel disturbance allowing leaked proteins to damage the brain within hours of immunisation, with no features of an encephalopathic illness, especially [illegible] caused by measles vaccine alone.

ta from this country, and from Sweden, show clearly, that whatever the trends in incidence of autism, they bear no relationship to the introduction of MMR vaccine (21, 22).

It is also clear from UK and French data that there is no increase in the incidence of Crohn's Disease in children with autism (23).

There is no evidence to indicate any link between MMR vaccine and autism. There appears to be no link between autism and Crohn's Disease or ulcerative colitis. It is possible that children with autism have a bowel disorder, and this warrants further examination.

What is the newly reported association of ileal-lymphoid nodular hyperplasia, autism, and MMR vaccine?

I have considered carefully the recent paper by Wakefield et al, published in the Lancet. This paper describes 12 children with ileal-lymphoid nodular hyperplasia. This condition has previously been described by Walker Smith, a co-author on the Lancet paper, as benign - "due to the frequency of its demonstration in asymptomatic children" (24). Other authors have found this condition to be common, occurring in 24% of barium follow-through examinations when investigating for suspected childhood chronic inflammatory bowel disease (25.26). Williams and Nicholls warn against misdiagnosis leading to inappropriate medication (27). Cumulative evidence suggests that this is indeed a benign condition, which disappears spontaneously, with no long-term sequelae (28). Since lymphoid nodular hyperplasia occurs commonly, it is not surprising that it occurred commonly in these autistic children, especially as they were referred to a paediatric gastroenterology unit.

Four children, of the twelve reported, were said to have abnormally low levels of some immunoglobulins and this observation was used to propose an increased susceptibility to the effects of the viruses in MMR. However, the reference ranges reported were for adult levels. If appropriate paediatric standards were used, only one child had a low IgA level, all of the

Much criticism has already been published of the biases inherent in the study, such that no reliability can be placed on the relevance of the association with MMR vaccine (29). Since the hypothesis offered to explain the mechanism for the neurodevelopmental problems of these children is inconsistent and biologically implausible, the purported link with MMR vaccine should be ignored.

This study has demonstrated normal variants in a highly selected sample, with no reason to believe that MMR vaccine played a part in their condition.

Should measles, mumps and rubella vaccines be given separately?

A number of parents have requested separate virus components rather than combined MMR vaccine, based on media reporting of the opinions of one of the RFH-IBDSG researchers. There is no evidence that MMR vaccine causes inflammatory bowel disease or autism, and there is no evidence that even if it did, giving the vaccines separately would prevent their occurrence. Since there is no evidence for such a risk from MMR vaccine, and it is clear that giving the vaccines separately would leave children and their contacts unnecessarily exposed to preventable infectious diseases and their consequences, I cannot endorse an opinion that jeopardises child health. Parents should realise that separating MMR vaccine into separate components is not, as has been portrayed, a safer option: on the contrary, it is a demonstrably riskier option.

Children should not be given separate measles, mumps and rubella vaccines in place of MMR, since there is no evidence for benefit and a clear risk of harm from following such a practice.

Kenneth C. Calman

Sir Kenneth Calman

References

1 Ekbom A et al. Crohn's disease after in-utero measles virus exposure. Lancet 1996; 348: 515-517.

2 Jones P, Fine P, Piracha S. Crohn's disease and measles [letter]. Lancet 1997; 349: 473.

3 Nielsen LLW et al. Exposure to measles in utero and Crohn's disease: Danish register study. BMJ 1998; 316: 196-7.

4 Thompson NP et al: Is measles vaccination a risk factor for inflammatory bowel disease? Lancet 1995; 345: 1071-1074.

5 Baxter T, Radford J. Measles vaccination as a risk factor for inflammatory bowel disease [letter]. Lancet 1995; 345: 1363.

6 Calman K. Measles vaccination as a risk factor for inflammatory bowel disease [letter]. Lancet 1995; 345: 1362.

7 Farrington P, Miller E. Measles vaccination as a risk factor for inflammatory bowel disease [letter]. Lancet 1995; 345: 1362.

8 MacDonald T. Measles vaccination as a risk factor for inflammatory bowel disease [letter]. Lancet 1995; 345: 1363.

9 Minor P. Measles vaccination as a risk factor for inflammatory bowel disease [letter]. Lancet 1995; 345: 1362-3.

10 Patriarca PA, Beeler JA. Measles vaccination and inflammatory bowel disease [Editorial]. Lancet 1995; 345: 1062-3.

11 Feeney M et al. A case control study of measles vaccination and inflammatory bowel disease. Lancet 1997; 350: 764-66.

12 Daszak P et al. Detection and comparative analysis of persistent measles virus infection in Crohn's disease by immunogold electron microscopy. J Clin Pathol 1997; 50: 299-304.

13 Wakefield AJ, Pittilo RM, Sim R. Evidence of persistent measles virus infection in Crohn's disease. *Journal of Medical Virology* 1993; 39: 345-353.

14 Liu Y et al. Immunocytochemical evidence of *Listeria*, *Escherichia coli* and *Streptococcus* antigens in Crohn's disease. Gastroenterology 1995: 108; 1396-1404.

References (continued)

15 Afzal MA et al. Absence of measles-virus genome in inflammatory bowel disease [research letter]. Lancet 1998; **351**: 646-7.

16 Haga y et al. Absence of measles viral genomic sequence in intestinal tissues from Crohn's disease by nested polymerase chain reaction. Gut 1996; **38**: 211-5.

17 Iizuka M et al. Absence of measles virus in Crohn's disease [letter]. Lancet 1995; **345**: 199.

18 Iizuka M, Masamune O. Measles vaccination and inflammatory bowel disease [letter]. Lancet 1997; **350**: 1775.

19 Fisher NC et al. Measles virus serology in Crohn's disease. Gut 1997; **41**(1): 66-9.

20 Touze I et al. IgM-specific measles virus antibody in families with a high frequency of Crohn's disease [letter]. Lancet 1995; 345: 967.

21 Nicoll A, Elliman D, Ross E. MMR vaccination and autism 1998: Déjà vu - pertussis and brain damage 1974? BMJ 1998; **316**: 715-6.

22 Gillberg C, Steffenburg S, Schaumann H. Is autism more common now than 10 years ago? British Journal of Psychiatry 1991; **158**: 403-9.

23 Fombonne E. Inflammatory bowel disease and autism [letter]. Lancet 1998; **351**: 955.

24 Walker Smith J, Hamilton JR. In Practical Paediatric Gastroenterology, 1983 ISBN 0-407-00204-9.

25 Lindley KJ, Milla PJ. Lancet 1998; 351:907.

26 Lipson A, Bartram CI, Williams CB et al, Barium studies and ileoscopy compared in children with suspected Crohn's disease. 1990. Clinical Radiology **41**: 5-8.

27 Williams CB, Nicholls S.Endoscopic features of chronic inflammatory bowel disease in childhood. Bailliere's Clinical Gastroenterology. 1994. 8;1: 121-131.

28 Theander G, Tragardh B. Lymphoid hyperplasia of the colon in childhood. 1976. Acta.Radiologica **17**: 631-648.

29 Chen RT, DeStefano F. Vaccine adverse events: causal or coincidental? [commentary] Lancet 1998; 351: 611-2.

Research letters

No evidence for measles, mumps, and rubella vaccine-associated inflammatory bowel disease or autism in a 14-year prospective study

Heikki Peltola, Annamari Patja, Pauli Leinikki, Martti Valle, Irja Davidkin, Mikko Paunio

Concern[1] of potential loss of confidence in measles, mumps, and rubella (MMR) vaccine has been raised by a recent paper[2] that suggested a causal association between this vaccine (or another environmental trigger) and a new syndrome of chronic inflammatory bowel disease and autism. Characteristically, all children described developed intestinal symptoms within days or soon after vaccination.

The National Board of Health and National Public Health Institute launched a long-term vaccination project in 1982, which aimed at the elimination of MMR diseases from Finland.[3] All children are vaccinated twice, at age 14–18 months and 6 years; further vaccinations are carried out among recruits of the defence forces and in some schools of nursing. Only one type of live-virus vaccine (MMR or Virivac [Merck, West Point, PA, USA]) consisting of the more attenuated Enders Edmonston, Jeryl Lynn, and Wistar RA 27/3 strains for measles, mumps, and rubella, respectively, has been used since beginning of the project. Adverse events in temporal relation to MMR vaccine were reported prospectively to the Institute. A form was filled and posted to us, followed by another form with further information 2–3 weeks later. We traced those vaccinees who developed gastrointestinal symptoms or signs lasting 24 h or more at any time after MMR vaccination (apart from within the first hour). We checked hospital or health centre records or interviewed the local public-health nurses.

By the end of 1996, about three million vaccine doses had been delivered by the Institute. 31 children developed gastrointestinal symptoms after vaccination (table); all except one after the first vaccine dose. *Haemophilus influenzae* type b conjugate vaccine was given concomitantly in four cases. 20 patients were admitted to hospital. Antibiotics were given in 11 cases, symptomatic relief in nine, and intravenous γ-globulin was given to one child with Guillain Barré syndrome.

The time between the reported event and our check on their health varied from 1 year and 4 months to 15 years and 1 month. The mean interval was 9 years 3 months, the median being 10 years and 8 months.

Diarrhoea, frequently with vomiting, was the most common symptom (55%, n=17), followed by gingivostomatitis (23%, n=7), vomiting only (16%, n=5), and abdominal pains (n=2). The time from MMR vaccine to onset of symptoms varied from 20 h to 15 days. Duration of symptoms was not always stated or recalled by nurses, but subsidence within a week was usual, except in a 1-year-old boy (patient 23) whose diarrhoea lasted for 6 weeks. The child recovered and was healthy when checked almost 6 years later. Most symptoms and signs of the central nervous system were those one would expect in conjunction with acute gastrointestinal disease: five (16%) children had febrile seizures and two had headache. One child developed ataxia

Child	Sex	Vaccination		Interval from vaccination to intestinal symptoms	Symptoms other than intestinal	Duration of intestinal symptoms	Admitted to hospital	Time elapsed until check-up
		Year	Age					
1	M	1982	6 yr 11 mo	~1 week	Fever, seizure, pneumonia	<1 week	Yes	11 yr 3 mo
2	F	1982	1 yr 9 mo	5 days	Fever, tonsillitis	3 days	Yes	9 yr
3	F	1982	6 yr 11 mo	1 day	Fever, headache	~4 days	No	7 yr
4	M	1982	1 yr 6 mo	2 days	Fever, respiratory	~1 week	Yes	5 yr 9 mo
5	F	1983	1 yr 5 mo	9 days	..	Not stated	Yes	15 yr 1 mo
6	F	1983	1 yr 2 mo	9 days	Fever, seizure	<2 days	Yes	15 yr 1 mo
7	M	1983	6 yr 11 mo	13 days	Fever	5 days	Yes	15 yr 1 mo
8	F	1983	6 yr 5 mo	10 days	Fever, otitis, headache	Not stated	No	14 yr 11 mo
9	M	1983	1 yr 6 mo	11 days	Fever, rash, pneumonia	Not stated	Yes	14 yr 9 mo
10	M	1983	1 yr 3 mo	13 days	Fever, seizure, rash	5 days	Yes	14 yr 8 mo
11	F	1983	1 yr 3 mo	4 days	Fever, rash	Not stated	Yes	14 yr 6 mo
12	F	1983	1 yr 3 mo	4 days	Fever, seizure, otitis	1 week	Yes	14 yr 5 mo
13	M	1983	2 yr 7 mo	8 days	Fever, lymphadenopathy	Not stated	No	13 yr 8 mo
14	F	1983	4 yr 6 mo	6 days	Fever, probable pneumonia	5 days	Yes	13 yr 7 mo
15	F	1984	3 yr 11 mo	20 h	Fever, rash	Not stated	Yes	14 yr
16	F	1984	1 yr 3 mo	3 days	Fever, seizure	1 week	Yes	13 yr 9 mo
17	M	1984	1 yr 7 mo	~2 weeks	..	Not stated	No	4 yr
18	M	1985	1 yr 4 mo	3 days	Fever, tonsillitis	Not stated	Yes	11 yr
19	M	1985	1 yr 9 mo	5 days	Fever, lymphadenopathy	Not stated	Yes	7 yr 11 mo
20	F	1986	6 yr 10 mo	3 days	Fever, pneumonia, otitis	3 days	Yes	11 yr 5 mo
21	M	1987	1 yr 7 mo	9 days	Fever, rash, conjunctivitis, otitis	~1 week	No	10 yr 8 mo
22	F	1989	2 yr 2 mo	4 days	Fever, respiratory	2 days	Yes	2 yr 10 mo
23	M	1991	1 yr 5 mo	7 days	Fever, rash, probable orchitis	6 weeks	No	5 yr 7 mo
24	F	1992	13 yr	3 days	Fever, urticaria, conjunctivitis	~2 days	No	6 yr 1 mo
25	F	1993	1 yr 2 mo	15 days	Urticaria	~2 days	Yes	4 yr 7 mo
26	M	1993	1 yr 5 mo	11 days	Fever, rash	6 days	No	4 yr 7 mo
27	M	1994	3 yr 9 mo	11 days	Fever, rash	~2 days	No	3 yr 8 mo
28	F	1995	1 yr 5 mo	5 days	Fever, ataxia	4 days	Yes	2 yr 7 mo
29	M	1995	1 yr 6 mo	13 days	Fever, urticaria	~2 days	No	1 yr 7 mo
30	F	1996	3 yr 7 mo	Not stated	Fever, rash	Not stated	Not stated	1 yr 9 mo
31	M	1996	1 yr 7 mo	11 days	Fever, Guillain Barré	5 days	Yes	1 yr 4 mo

Characteristics of patients with gastrointestinal and other symptoms after MMR vaccination

which subsided quickly. No child developed autistic-spectrum disorder. Hyperornithaemic gyrate atrophy, an autosomal recessive disease, was diagnosed in one girl (patient 14) 8 years after vaccination. A boy developed *H influenzae* meningitis, and a girl meningococcal meningitis 1 day and 7 days after vaccination, respectively.

It is noteworthy that, besides gastrointestinal complaints, many children had similar symptoms and signs (fever, rash, seizure) as those in London.[2] Presumably, some patients with symptoms or signs not far from those listed in the table were not reported to us. We do not deem this shortcoming to be of a major concern because illness in all our 31 patients was mild, and probably sometimes caused by concomitant infection.[4]

Over a decade's effort to detect all severe adverse events associated with MMR vaccine could find no data supporting the hypothesis that it would cause pervasive developmental disorder or inflammatory bowel disease.

We thank Tapio Kurki, Olli P Heinonen, Kari Cantell, and Viena Karanko, and Irja Davidkin for their contribution. The study was partly funded by a grant by Merck Research Laboratories, West Point, PA, USA.

1 Lee JW, Melgaard B, Clements CJ, et al. Autism, inflammatory bowel disease, and MMR vaccine. *Lancet* 1998; 351: 905–09.
2 Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998; 351: 637–41.
3 Peltola H, Heinonen OP, Valle M, et al. The elimination of indigenous measles, mumps, and rubella from Finland by a 12-year, two-dose vaccination program. *N Engl J Med* 1994; 331: 1397–402.
4 Tait DR, Ward KN, Brown DWG, Miller E. Measles and rubella misdiagnosed in infants as exanthem subitum (roseola infantum). *BMJ* 1996; 312: 101–02.

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Severe premature coronary artery disease with protease inhibitors

Keith Henry, Holly Melroe, Jacquelyn Huebsch, Jessica Hermundson, Claudia Levine, Lyle Swenson, Jack Daley

Until recently, the prognosis for people with AIDS was so poor that concerns about other long-term health problems seemed irrelevant. The introduction of antiretroviral treatment with protease inhibitors has had a profound impact on mortality from AIDS.[1] After two young AIDS patients on protease inhibitors under our care developed coronary artery disease, we examined lipid abnormalities among HIV-1-infected people receiving protease inhibitors and designed an intervention based on the National Cholesterol Education Program (NCEP) guidelines.[2]

A 26-year-old HIV-1-infected man (CD4 T cell count <10 cells/μL) was admitted with angina. He had a history of cigarette smoking and occasional cocaine use (none recently). The plasma HIV-1-RNA level was more than 1 000 000 copies/mL, so 4 weeks before admission he was started on directly-observed ritonavir, saquinavir, lamivudine, and stavudine. Coronary angiography showed a large occlusive thrombus within the right coronary artery.

A 37-year old HIV-1-infected man presented with angina after shovelling snow. His lowest CD4 T-cell count was 14 cells/μL with a peak plasma HIV-1 RNA level of 685 000 copies/mL. He had developed cytomegalovirus retinitis and diabetes mellitus before starting protease inhibitors at age 35. He had a family history of heart disease but no history of cigarette smoking. His cholesterol concentration increased from 4·28 mmol/L before starting indinavir to 8·46 mmol/L 5 months later. 7 months before presentation his fasting cholesterol was 12·3 mmol/L, high-density cholesterol (HDL) 0·46 mmol/L, and triglycerides 22·14 mmol/L, while his plasma HIV RNA level was <500 copies/μL. He developed a right cervical region fat pad. He was taking gemibrozil 600 mg orally twice daily, aspirin, indinavir, zidovudine, and lamivudine. Coronary arteriography revealed occlusion of the left anterior descending artery and severe atherosclerosis involving the right coronary artery.

A review of 124 patients on protease inhibitors in our HIV clinic identified 41 (33%) with raised lipid concentrations who were referred for NCEP intervention. For 15 patients (mean fasting lipids-cholesterol 6·35 mmol/L; triglycerides 3·6 mmol/L), a diet exercise programme was instituted. 26 patients (mean fasting lipids-cholesterol 8·98 mmol/L; mean triglycerides 19·2 mmol/L) were referred for drug treatment (gemfibrozil for 3 months then atorvastatin).

Peripheral lipodystrophy has been reported in patients receiving protease inhibitors.[3,4] In one study, metabolic abnormalities (higher triglyceride, cholesterol, insulin, and C-peptide levels, and insulin resistance scores) were described in 72 (64%) of 116 patients after a mean 10 months on treatment.[5] Clinicians need to be aware of the potential for accelerated atherosclerosis in patients treated with protease inhibitors. For now, we obtain a fasting lipid profile before and then 3–6 months after the start of protease inhibitor therapy and then use NCEP guidelines to treat abnormalities identified.

1 Cameron DW, Heath-Chiozzi M, Danner S, et al. Randomised placebo-controlled trial of ritonavir in advanced HIV-1 disease. *Lancet* 1998; 351: –49.
2 National Institutes of Health. Cholesterol lowering in the patient with coronary artery disease: physician monograph-national cholesterol education program. September 1997 (NIH Publication 97-3794).
3 Mann M, Piazza-Hepp T, Koller E, Gibert C. Abnormal fat distribution in AIDS patients following protease inhibitor therapy. FDA summary. In: Programs and Abstracts of the 5th National Conference on Retroviruses and Opportunistic Infections; Chicago, Illinois, Feb 1–5, 1998 (abstr 412).
4 Miller K, Jones E, Yanovsky J, Shankar R, Feuerstein I, Falloon J. Visceral abdominal-fat associated with use of indinavir. *Lancet* 1998; 351: 871–75.
5 Carr A, Samaras K, Burton S, Freund, J, Chisholm DJ, Cooper DA. A syndrome of peripheral lipodystrophy and insulin resistance due to HIV protease inhibitors. In: Programs and Abstracts of the 5th National Conference on Retroviruses and Opportunistic Infections; Chicago, Illinois: Feb 1–5, 1998 (abstr 410).

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Hormone-receptor status of breast cancer in Papua New Guinea

Aolhopo Pip, David Watters, Datti Murthy, Nick Wood, Peter Donnelly

The survival of women with breast cancer varies with racial background and geographical location. Whilst black women have a higher mortality than white women, the causes of racial difference in breast tumour biology are unknown.[1] The well-known association between oestrogen (ER) and progesterone (PR) receptor status and both response to tamoxifen treatment and prognosis has prompted several

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GLOBAL PROGRAMME FOR VACCINES AND IMMUNIZATION
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World Health Organization
Geneva
1998

1.5.2 Measles, MMR, Crohn's disease and autism—Dr D. Salisbury

Hypothesis 1. Early measles infection linked to inflammatory bowel disease (IBD). Measles virus-like particles were said to be detected by researchers at the the Royal Free Hospital School of Medicine Inflammatory Bowel Disease Group by immunohistochemical staining, *in situ* hybridization and immunogold electron microscopy.

> Discussion. Three groups of researchers found no evidence of detectable virus genome in clinical specimens from patients with inflammatory bowel disease using highly sensitive molecular approaches such as the reverse transcriptase polymerase chain reaction (RT-PCR) technique. Analysis of serum from patients with Crohn's disease and of measles virus IgM by ELISA found no evidence for a role of measles virus in the aetiology of Crohn's disease.

Hypothesis 2. Exposure to measles in pregnancy or perinatal period presents a risk for Crohn's disease and ulcerative colitis. A case series of four mothers and children from Sweden suggested that infection during pregnancy may adversely affect foetuses increasing the risk of Crohn's disease in the offspring.

> Discussion. Two case control studies, one from Denmark and the other from the United Kingdom, have not found an association between measles in pregnancy and IBD. In the United Kingdom case-control study involving 47 individuals, no cases of IBD were found in the subjects exposed to measles *in utero*, although one case of Crohn's and one case of ulcerative colitis were found in controls.

Hypothesis 3. Live attenuated measles vaccine is associated with increased risk of Crohn's disease. The significant differences in the rates of Crohn's disease and ulcerative colitis between people receiving active immunization with measles vaccine and unvaccinated controls provide evidence that measles vaccine virus has a role in the aetiology of IBD. One study by Thompson et al. that compared a cohort of immunized children from 1964 with an unimmunized cohort from 1958 suggested an increased risk of Crohn's disease in the immunized cohort.

> Discussion. An increase of Crohn's disease predates measles vaccine. Recent incidence goes flat in under 20s who have had measles vaccine. The study by Thomson et al. has been severely criticized regarding the selection of cases with unmatched controls, differential drop-out rates in the two groups, and different means of case ascertainment. Another case-control study by the East Dorset Gastroenterology Group showed no link between live attenuated measles vaccination and the subsequent risk of developing either Crohn's disease or ulcerative colitis.

Hypothesis 4. MR and MMR are risk factors for Crohn's disease, and the three viruses given together have harmful effects. The long-lasting immunosuppressive qualities of the measles virus indicates that viral interaction may be plausible constituting a higher risk of developing Crohn's disease. It has been alleged that "the incidence of Crohn's disease has increased since 1994 MR campaign"; and that "since the introduction of MMR in 1988, the risk of IBD has increased threefold."

Discussion. The immunosuppressive effect of measles vaccine is slight. Data from Oxford and Finland studies show that no increase in Crohn's disease were linked with the introduction of MMR immunization. In 1994, approximately seven million children received a combined measles and rubella vaccine. Data from hospital episode statistics show no increase in new cases or exacerbation of existing cases of Crohn's disease following immunization campaign. MMR has been used for 25 years in the US; more than 150 million doses have been administered with no evidence to support allegation of harm. There is no biologically plausible mechanism; each virus elicits its effects at different times.

Hypothesis 5 .MMR is a risk factor for autism. The incidence of autism has increased since the introduction of MMR, especially regressive autism. A Member of Parliament (United Kingdom), declared in a parliamentary debate in 1997: "The work of three researchers has proven a link between MMR vaccine and autism."

Discussion. The actual incidence of autism is uncertain, since diagnostic criteria have changed in recent years and children whose conditions were diagnosed as other than autism in the past are now likely to be included within autistic spectrum disorder. Autism, with developmental regression, was well recognized before MMR vaccine was available, and children may present in this way with signs of regression being recognized both before and after receipt of MMR vaccine.

The first signs of an autism-like disorder generally appear in the second year of life. This coincides with the time when most children receive their MMR vaccine. Such coincidence does not imply a causal link. Data from the United Kingdom and from Sweden, clearly show that whatever the trends in incidence of autism, they bear no relationship to the introduction of MMR vaccine. It is also clear from United Kingdom and French data that there is no increase in the incidence of Crohn's Disease in children with autism.

There is no evidence to indicate any link between MMR vaccine and autism, in the threeresearch studies mentioned. The author of one study declared "My studies have not scientifically addressed this issue." The second study reported that, since autism has never been linked with measles vaccine, there is no biological plausibility to admit that rubella and mumps components of MMR have caused a bowel disturbance allowing leaked proteins to damage the brain within hours of immunization. In the third study, cases after MMR did not have urinary excretion of 'substance specific for autism'.

Hypothesis 6. A recent paper published in Lancet that included investigations in 12 autistic children reported an association between ileal-lymphoid-nodular hyperplasia, non-specific colitis and developmental regression and MMR vaccine.

Discussion. Ileal-lymphoid nodular hyperplasia is common, occurring in 24% of barium follow-through examinations when investigating for suspected childhood chronic inflammatory bowel disease. Cumulative evidence suggests that this is indeed a benign condition, which disappears spontaneously, with no long-term sequelae. Since lymphoid nodular hyperplasia occurs commonly, it is not surprising that it occurred commonly in these autistic children, especially as they were referred to a paediatric gastroenterology unit. Four children, of the twelve reported, were said to have abnormally low levels of some immunoglobulins and this observation was used to propose an increased susceptibility to the effects of the viruses in MMR. However, the reference ranges reported were for adult levels. If appropriate paediatric standards were used, only one child had a low IgA level. All of the remaining values were within normal ranges. Much criticism has already been published on the biases inherent in the study, such that no reliability can be placed on the relevance of the association with MMR vaccine. The hypothesis explaining the mechanism for the neurodevelopmental problems of these children is inconsistent and biologically implausible.

Conclusion: Measles, MMR, Crohn's Disease, and Autism

More than 30 experts met at the Medical Research Council (MRC) on 23 March 1998 to consider the available data relating to a possible link between measles virus infection, inflammatory conditions of the bowel, and autism. Evidence was presented in the fields of virology, epidemiology and gastroenterology. Conclusions were considered and conveyed to the Chief Medical Officer for England.

The MRC expert group concluded:

(1) Available virological and epidemiological evidence does not support a causal role for persistent measles virus infection and Crohn's disease.

(2) There is no evidence to indicate any link between MMR vaccination and bowel disease or autism.

(3) A better understanding of the causes of Crohn's disease and autism is needed. The Royal Free Hospital School of Medicine (where the studies on Crohn's disease and autism were conducted) has agreed that the Department of Health should not alter its present policy for the vaccination of children with MMR.

Handling of problem

Anticipatory

- Efforts to stimulate national and international studies to examine proposed hypotheses.
- Reviews by national advisory committee.
- Review by independent experts via MRC—agenda arranged by The Royal Free Hospital School of Medicine Inflammatory Bowel Disease Group.

Responsive

- Letter from the Chief Medical Office to all doctors.
- Active response to media enquiries.
- New, reassuring advertising and materials.

Lessons learned

- The media are attracted to scare stories and may appear to champion single workers against the establishment.
- The support of international agencies, e.g., WHO, is very helpful.
- Unlike the pertussis scare of the 1970s, answers were obtained in parallel, not in series.

①

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COMMITTEE ON SAFETY OF MEDICINES

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IN THIS ISSUE: Page No.

The safety of MMR vaccine 9

Insert: Leaflet for parents on MMR vaccine

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The safety of MMR vaccine

Suggested associations with autism and Crohn's disease are not supported by a detailed review of cases and a new epidemiological study

On the basis of their research findings, a group at the Royal Free Hospital, London led by Dr Andrew Wakefield has suggested that both measles infection and measles vaccination may be associated with an increased risk of Crohn's disease, and that MMR vaccine may be associated with the development of autism (a disorder frequently diagnosed in the second year of life). MMR vaccine was introduced into the routine UK immunisation programmes in 1988, since when around 10 million immunisations have been given to children at the age of 13-15 months, as well as at 4 years of age.

All the available evidence relevant to these concerns has been carefully reviewed by the independent expert committees which routinely advise on the safety of medicines and on immunisation policy (the Committee on Safety of Medicines and the Joint Committee on Vaccination and Immunisation) and by an independent expert group convened in March 1998 by the Medical Research Council (MRC). The view of all these groups is that the evidence cited by Wakefield and colleagues does not support the concerns raised. However, it is inevitably difficult to refute completely such claims and they have understandably caused concern to parents and health professionals. In particular, there is a substantial number of individual reports from parents who believe that MMR vaccine is responsible for the subsequent development of autism or Crohn's disease in their children. During 1996-7 the Medicines Control Agency was informed by a firm of solicitors that they had received several hundred such reports. A wide variety of other conditions had also been reported.

CSM Working Party

In order that more information could be obtained about these possible adverse effects, purpose-designed questionnaires were sent to parents via the solicitors. To validate information received from parents, further questionnaires were sent to the doctors (the GP and at least one specialist) who had cared for these children.

On the advice of the Committee on Safety of Medicines, a Working Party was formed to assess these parental reports together with medical evidence received from the GPs and specialists. The Working Party included members with specialist expertise in the fields of gastroenterology, general paediatrics, paediatric neurology and child psychiatry. Based on their review of case information described above, the Working Party reached the conclusions shown in the box overleaf.

Conclusions of the Working Party on MMR Vaccine

1. The exercise undertaken in respect of cases of children with adverse effects attributed by parents to MMR or MR vaccine and reported to a firm of solicitors has yielded a considerable volume of medical information which was extremely variable in quality and completeness.

2. The information evaluated has important intrinsic limitations as regards assessing whether the vaccines are, or are not, causally associated with the attributed adverse effects. Notably these are: bias in the selection of cases for which it would be impossible to compensate, and a lack of any control (unimmunised) group with which the frequency and characteristics of the attributed illnesses could be compared. Also there was frequent divergence between parents and doctors regarding specific details of the illnesses.

3. Detailed evaluation of 92 cases with autism and all 15 cases with confirmed Crohn's disease revealed no extraordinary features which suggested a novel syndrome, nor did it support causal associations with MMR or MR vaccines. In particular, no case of autism developed following an acute unexpected and/or unexplained neurological event in the post-vaccination period.

4. For only 8 cases of the 92 with autism and 4 of the 15 with Crohn's disease was satisfactory evidence available to infer (i) medical confirmation of the diagnosis (ii) a close temporal association between administration of the vaccine and onset of the illness (iii) no relevant prior history and (iv) absence of an alternative cause. The numbers of such cases identified was therefore small. Furthermore these factors alone are insufficient to prove causation, particularly as the onset of autism is frequently recognised around the time MMR vaccine is given. The pattern of the illnesses reported for the 8 cases with autism and 4 with Crohn's disease cited above did not appear to differ from that of other children with these disorders. There was no evidence to suggest that administration of MMR or MR vaccine was associated with particular variants of pervasive developmental disorder or inflammatory bowel disease.

5. It was impossible to prove or refute the suggested associations between MMR vaccine and autism or inflammatory bowel disease because of the nature of the information, the self-selection of cases and the lack of comparators. Nevertheless, the Working Party found that the information available did not support the suggested causal associations or give cause for concern about the safety of MMR or MR vaccines.

Epidemiological evidence

Evidence from other countries does not support an increased incidence of autism or Crohn's disease which can be attributed to the introduction of MMR vaccine[1,2,3]. However, in order to further study the suggested association with autism, the Medicines Control Agency commissioned an epidemiological study in the North Thames region which has recently been completed and is published in *The Lancet* this weekend[4]. This study linked diagnostic information from clinical records with independently collected immunisation data. The study indicates that there was no sudden "step-up" or change in the incidence trend line of autism after the introduction of MMR vaccine. In individual cases, the age of diagnosis was not related to vaccination status and there was no clear temporal clustering of new cases of autism in relation to immunisation. The authors concluded that their analyses did not support a causal association between MMR vaccine and autism.

Conclusions

The review conducted by the Working Party and the North Thames study provide important new evidence which was not available when the MRC expert group was convened. Neither supports the hypothesis that MMR or MR vaccines are causally associated with autism or Crohn's disease. On the basis of all the available evidence, the demonstrated benefits of MMR or MR vaccines far outweigh any possible risks.

The enclosed information leaflet may be helpful in discussions with concerned parents, in order to provide reassurance.

The full report of the MMR Working Party is available on the MCA/CSM web-site or, alternatively by writing to the Pharmacovigilance Support Unit, Room 1001, Market Towers, 1 Nine Elms Lane, London SW8 5NQ.

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1. Nielsen LJ.W et al British Medical Journal 1998, 316: 196-7
2. Peltola HG et al British Medical Journal 1998, 316 1745
3. Gillberg C et. al. British Journal of Psychiatry 1991; 158 403-9
4. Taylor B. et. al. Lancet, in press, 12 June 1999.

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Message No. Page 1 of 1 pages Date: 9 June 1999

From: Director,
Vaccines and Other Biologicals

To: Dr David M. Salisbury
Principal Medical Officer
Department of Health
London

Fax No.: 44 171 972 4468

Our ref.: I1/446/13

Subject: REPORTS

TEXT

Dear Dr Salisbury,

Thank you for sharing with us the two reports which looked at the possible association between administration of MMR vaccine and the occurrence of variants of pervasive development disorder (autism) and inflammatory bowel disease (IBD). The World Health Organization, like the Department of Health in the United Kingdom, is interested in learning of any suggestion that a vaccine might not be safe.

Having reviewed the papers by Taylor et al (1) and the Working Party of the Committee on Safety of Medicines (2), we note that they are accurate and add further to the scientific evidence already existing. There is no link between the vaccines containing measles (particularly MMR) and these two groups of diseases. The reports represent another step in strengthening the position of WHO which we have already publicly stated (3).

We remain open to any fresh scientific evidence that might be generated to provide new insights. The current evidence clearly demonstrates however that there is no proof of association between administration of MMR and these two clinical entities. It would be morally indefensible of WHO to do anything other than continue promoting the widespread use of these vaccines which save million of lives each year, and prevent millions more from suffering terrible complications of the diseases.

Yours sincerely,

References

1. Taylor B et al. Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association.
2. Committee on Safety of Medicine. Report of the working party on MMR vaccine. HMSO London 1999.
3. Lee JW, Melgaard B, Clements CJ, Kane M et al. Autism, inflammatory bowel disease and MMR vaccine. Letter to the editor. Lancet 351; 905, 1998

Signed: Dr Bjorn Melgaard

Copies to: Dr P. Duclos, VAM
Dr R. Chen, ATT
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THE NATIONAL
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THE NATIONAL AUTISTIC SOCIETY

POSITION STATEMENT

MMR and AUTISM

The National Autistic Society welcomes the new studies, commissioned by the Committee on the Safety of Medicines, which sought to establish whether there was a connection between measles, mumps and rubella (MMR) vaccines and later autism. The authors of the 10-year retrospective study of children with an autistic spectrum disorder in the North Thames region concluded that there was no association between autism and the vaccine (to be published in *The Lancet*, 9 June 1999). A smaller scale study of 200 children (to be reported in *Current problems in pharmacovigilance)* similarly found no association.

Parents are often confused by media reports on this subject. A leaflet summarising the issues is available from the Health Education Authority. However, the NAS has been contacted by large numbers of parents concerned about the possibility of their child contracting an autistic spectrum condition following the MMR vaccination. If parents are still concerned about the possible risks (particularly if they already have a child with autism or the child to be vaccinated already shows some risk factors) they should consult their GP for further advice. The National Autistic Society shares parents' concerns that vaccines used should be as safe as is possible.

The general medical consensus, supported by the Department of Health and the World Health Organisation, is that childhood immunisation has provided vast benefits to millions of people both in the UK and world-wide and should be continued. The general medical advice is to have children vaccinated.

It is difficult to assess temporal trends in the incidence of autism due to changes in referral pattern and diagnostic criteria. More basically, however, the epidemiological data is simply not collected in the UK. The National Autistic Society would welcome the collection of epidemiological data on the incidence of autistic spectrum disorders. Rigorous epidemiological study of large populations of children would help to resolve the many questions of prevalence and causation in autism.

Date: 10.06.99

Patron: *HRH The Princess Royal* Chairman: *Judy Lasty*
President: *Jane Asher* Chief Executive: *Paul Cann*

BUILDING A BRIGHTER FUTURE
FOR PEOPLE WITH AUTISM

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PRESS RELEASE

● Go back to referring page ● Main Page

1999/0342

Thursday 10th June 1999

TWO NEW INDEPENDENT STUDIES FIND NO LINK BETWEEN MMR VACCINATION AND AUTISM

Two new independent studies have not found a link between MMR vaccination and autism, Dr Jeremy Metters, the Deputy Chief Medical Officer said today.

The first study, undertaken by a specially convened independent Working Party on MMR vaccine set up by the Committee on Safety of Medicines, examined records passed to the CSM by a firm of solicitors where there was said to be an association between MMR or MR vaccine and autism or Crohn's disease.

A total of 92 cases of autism and 15 cases of Crohn's disease were systematically reviewed. Parents filled in questionnaires and medical reports were obtained from the children's GPs and specialists.

The Working Party concluded that the evidence "did not support the suggested causal associations or give cause for concern about the safety of MMR or MR vaccines". The experts believed that there was no new syndrome causing autism or Crohn's disease after MMR vaccination. This conclusion has been endorsed by the CSM.

The second was an epidemiological study, carried out by a team from the Royal Free Hospital and the Public Health Laboratory Service. This investigated the history of all 498 known autistic children born in North Thames since 1979 - covering the period before and after the introduction of MMR vaccination in 1988. The study, published in the Lancet today, found:

no increase in autism since the introduction of MMR in 1988;
no difference in age of diagnosis between MMR immunised and unimmunised children;
no difference in the MMR immunisation rates between those children with autism and the general population;
no link between the timing of MMR and the onset of autism.

The authors concluded that: "No causal associations could be found between MMR and autism".

Welcoming these reassuring findings, Dr Metters said:

"These two new studies add to the substantial body of evidence already showing there is no link between MMR and autism or Crohn's disease. These studies confirm the conclusions of 37 independent experts, convened by the Medical Research Council last year, who found no evidence of any link and every subsequent major piece of work, including studies in Finland and Sweden, has reached the same conclusion.

"The Department of Health has a duty to provide the best and safest protection for the nation's children, and MMR vaccination offers the best means of protecting children from diseases that can still cause severe disability and even death.

"Our aim is to ensure that children are protected and it is vital that confidence in MMR, a key part of our childhood immunisation programme, is maintained and, where confidence has been called in question, restored as soon as possible.

"It is natural for parents to worry about the health and wellbeing of their children. The studies published today offer further reassurance and confirmation to those who are concerned about the possibility of a link. The fact is MMR vaccination does not cause autism or Crohn's disease.

"The alleged association between MMR and autism or Crohn's disease has now been reviewed by the Committee on Safety of Medicines (CSM), the Joint Committee on Vaccination and Immunisation and the Medical Research Council. All these found independently no evidence of a causal link between MMR and either Crohn's disease or autism.

"There is no scientific basis that justifies putting children at risk either by failing to have them immunised or by giving them three single injections that leave children partially unprotected. Such methods will not protect children from autism or Crohn's disease, but they will be put at risk from the very diseases MMR vaccination prevents."

Notes to Editors

1. MMR is a combined vaccine usually given to children between 12 and 15 months of age and again at around four years, as protection against measles, mumps and rubella. MMR was introduced into the UK immunisation programme in 1988 and has substantially reduced the incidence of death and disability due to these three infections. A combined measles and rubella vaccine (MR) was given to 90 per cent of children aged five to 16 in October 1994 to avert an anticipated epidemic.

2. Autism is a developmental disorder that usually appears in the second year of life. It affects social interactions, communication, body movement and can lead to lack of involvement in social activities and delays in development.

3. Crohn's disease is an inflammation of the intestine that may cause symptoms of diarrhoea, abdominal pain, weight loss and passing blood in the stools. Patients may need to take tablets or require surgery.

4. The CSM is an independent committee of experts that advise Government on the safety, quality and effectiveness of medicines, including vaccines. The Joint Committee on

Vaccination and Immunisation is an independent statutory committee which advises United Kingdom Health Ministers on immunisation policy.

5. The Working Party on MMR vaccine, chaired by Professor Michael Langman, Professor of Medicine at the University of Birmingham, was set up by the CSM to review reports of suspected autism and Crohn's disease from parents of affected children who had contacted a firm of solicitors. Detailed review of the reports included questionnaires completed both by parents and doctors (GPs and specialists) for each child.

6. The findings of the Working Party were published today in Current Problems in Pharmacovigilance and reported in summary in the Lancet. The full report is available on the internet at: http://www.open.gov.uk/mca/cuprblms.htm

[ENDS]

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This page last updated 22 June 1999

DEPARTMENT OF HEALTH

Press release

1999/0342

Thursday 10th June 1999

Embargoed until 00:01:00 on Friday 11th June 1999

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[ENDS]

Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association

Brent Taylor, Elizabeth Miller, C Paddy Farrington, Maria-Christina Petropoulos, Isabelle Favot-Mayaud, Jun U, Pauline A Waight

Summary

Background We undertook an epidemiological study to investigate whether measles, mumps, and rubella (MMR) vaccine may be causally associated with autism.

Methods Children with autism born since 1979 were identified from special needs/disability registers and special schools in eight North Thames health districts, UK. Information from clinical records was linked to immunisation data held on the child health computing system. We looked for evidence of a change in trend in incidence or age at diagnosis associated with the introduction of MMR vaccination to the UK in 1988. Clustering of onsets within defined postvaccination periods was investigated by the case-series method.

Findings We identified 498 cases of autism (261 of core autism, 166 of atypical autism, and 71 of Asperger's syndrome). In 293 cases the diagnosis could be confirmed by the criteria of the International Classification of Diseases, tenth revision (ICD10: 214 [82%] core autism, 52 [31%] atypical autism, 27 [38%] Asperger's syndrome). There was a steady increase in cases by year of birth with no sudden "step-up" or change in the trend line after the introduction of MMR vaccination. There was no difference in age at diagnosis between the cases vaccinated before or after 18 months of age and those never vaccinated. There was no temporal association between onset of autism within 1 or 2 years after vaccination with MMR (relative incidence compared with control period 0·94 [95% CI 0·60–1·47] and 1·09 [0·79–1·52]). Developmental regression was not clustered in the months after vaccination (relative incidence within 2 months and 4 months after MMR vaccination 0·92 [0·38–2·21] and 1·00 [0·52–1·95]). No significant temporal clustering for age at onset of parental concern was seen for cases of core autism or atypical autism with the exception of a single interval within 6 months of MMR vaccination. This appeared to be an artifact related to the difficulty of defining precisely the onset of symptoms in this disorder.

Interpretation Our analyses do not support a causal association between MMR vaccine and autism. If such an association occurs, it is so rare that it could not be identified in this large regional sample.

Lancet 1999; 353: 2026–29
See Commentary page 1987

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Correspondence to: Prof Brent Taylor

Introduction

Wakefield and colleagues[1] postulated that measles, mumps, and rubella (MMR) vaccination might be causally linked with autism. Although there is no scientific evidence to support this claim,[2-4] neither are there robust data on the prevalence of autism in children born before and after the introduction of MMR vaccine to the UK in 1988. The postulated causal link between MMR vaccination and autism was based on a reported close temporal association between these two events.[1] Since MMR vaccine is given at around 12–15 months of age and the mean age at which parents of children with autism first report concern about their child's development is 18–19 months,[5] a close temporal association in some autistic children would be expected by chance.[6]

We undertook a population-based study in the North East Thames region to investigate trends in the incidence of autistic disorders before and after the introduction of MMR vaccine in October, 1988, and the immunisation histories of children with these disorders. We used case-series analysis methods to test for clustering of onsets within defined postvaccination periods.

Patients and methods

Children with autistic disorders born since 1979 were identified in eight health districts in mid-1998 from computerised special needs/disability registers at child development centres and from records in special schools. Information on children with such disorders who were younger than 16 years of age was extracted from clinical records by one of three experienced paediatric registrars. The information extracted included the age at which the autistic disorder was diagnosed, the recorded age at which the parents first became concerned about the child's developmental state, and the age at which the regression became obvious, if that was a feature.

By use of criteria of the International Classification of Diseases, tenth revision (ICD10), the diagnosis of autism was checked against information in the available records on the child's present condition and his or her condition between the ages of 18 months and 3 years. Study investigators worked in pairs with opportunity for discussion to reach consensus when there was ambiguity. Inter-rater reliability was tested on 20 case records (independent completion of the data-collection form); the concordance was above 95%. Immunisation data, which were recorded independently of the clinical record, with exact dates, were obtained from the Regional Interactive Child Health Computing System (RICHS).

Three statistical analyses were undertaken. First, trends in the time series of cases were analysed by Poisson regression. Because of delays in diagnosis, ascertainment of cases in later years is incomplete. To circumvent this problem, only cases aged 0–59 months at diagnosis and born in the years 1979–92 were included in this analysis. We looked for evidence of a change after 1987, first by allowing a "step-up" in the 1987 and later birth cohorts and second by allowing the exponential trends to differ before and after 1987.

Second, the age at diagnosis was compared in vaccinated and unvaccinated children with autism diagnosed after the age of

Variable	Core autism (n=261)		Atypical autism (n=166)		Asperger's syndrome (n=71)	
	n	Median (months)	n	Median (months)	n	Median (months)
Age at diagnosis	235	37	122	42	67	73
Age at parental concern	207	19	119	21	48	24
Age at regression	75	18	30	18	4	30
Interval concern to diagnosis	235	22	122	26	67	53
Interval regression to diagnosis	73	17	27	17	4	14·5

n=number of cases for whom information was available.

Table 1: Median (in elapsed months of age) for age at diagnosis, age at parental concern, and age at regression, and intervals between these, according to diagnostic category

18 months. Children were classified into three categories: those who had received MMR vaccine before the age of 18 months; those never vaccinated with MMR; and those who had received MMR vaccine at age 18 months or later. Because of the skewed distribution of the age at diagnosis of autism, the analysis was done on logarithms of age, with linear regression to compare the mean log ages in the three vaccine categories, and with control for the effect of birth cohort.

Third, possible temporal associations between vaccinations and the age at diagnosis of autism, the recorded age at parental concern, and the age of onset of regression were analysed by the case-series method.[3-4] This method is valid for rare chronic disorders of acute onset. For autism diagnosis, we investigated periods within 1 or 2 years after vaccination as the risk periods. For date at parental concern, we looked at periods of within 6 months or 1 year after vaccination. Because of the suggestion that regression may be an acute event after vaccination[1] we considered periods of within 2 months, 4 months, and 6 months of vaccination. Where vaccination and the event of interest occurred in the same month, we assumed that vaccination preceded the event. Two analyses were done for each combination of endpoint and risk period; the first took into account only MMR vaccine, with single-antigen measles vaccine and combined mumps and rubella vaccine ignored; and the second included all three types of vaccine. In each analysis, the reference period for each individual consisted of every month from birth to the end of August, 1998, that did not fall during a postvaccination risk period. All analyses were finely stratified for age, particularly in younger age-groups, because of the multimodal age distribution of recorded events. 17 age-groups were used for autism diagnosis, 30 for parental concern, and 21 for regression.

Results

498 children with autism were identified: 261 with typical (core) autism (prevalence rate in children under 16 years of age 5·3 per 10 000), 166 (3·4 per 10 000) with atypical autism, and 71 (1·4 per 10 000) with Asperger's syndrome. The diagnosis could be confirmed with ICD10 criteria, from information recorded in the clinical notes, in 214 (82%) cases of core autism, 52 (31%) cases of atypical autism, and 27 (38%) cases of Asperger's syndrome. 441 (89%) children were documented as having been assessed by a neurodevelopmental paediatrician, 411 (83%) by a speech therapist, and 422 (85%) by a child psychiatrist or a clinical or educational psychologist. 192 (39%) were recorded as having also been assessed at a centre specialising in autism.

The median ages at diagnosis, first parental concern, and regression according to diagnostic category are shown in table 1. Age at parental concern showed big peaks at 18 months and 24 months for core and atypical autism. With one exception, the earliest age at diagnosis was 18 months in the core and atypical autism groups and 30 months in the Asperger's syndrome group.

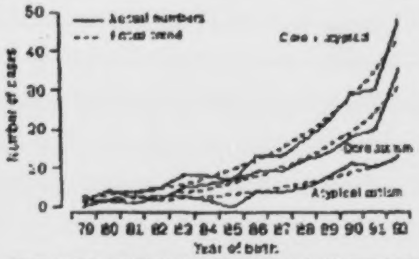

Figure 1: Core and atypical autism cases under 60 months of age and fitted trends by year of birth 1979–92

Regression was recorded for 29% of core autism cases compared with 18% of atypical cases and 6% of those with Asperger's syndrome.

The number of cases by year of birth showed a steady rise peaking in the early to mid 1990s, followed by a sharp decline that was most pronounced for cases of core and atypical autism. This decline is attributable to delays in diagnosis inherent in the disorders. There was a significant upward trend over the period 1979–92 for core and atypical cases (test for zero trend p<0·001) and a nearly significant upward trend for Asperger's syndrome (p=0·06). For the core and atypical cases, there was no evidence of a sudden "step-up" in 1987, the first birth cohorts eligible for MMR vaccine in the second year of life (p>0·25). Neither was there evidence that the exponential trend changed after 1987 (figure 1).

A total of 389 children with core autism, atypical autism, or Asperger's syndrome were born after 1987; 336 (86·4%) of these had received MMR vaccine by the end of the second year of life and a further 17 (4·4%) received the vaccine after this age. The modal age at which MMR vaccine was given was 13 months. The MMR vaccine coverage in the 389 study cases did not differ significantly from that in the same birth cohorts in the North East Thames region as a whole (figure 2). Trends in the incidence of autism by birth cohort since 1987 (figure 1) were not temporally associated with changes in vaccine coverage (figure 2). Owing to the small numbers of Asperger's cases eligible for MMR vaccine in the second year of life (49), and their older age

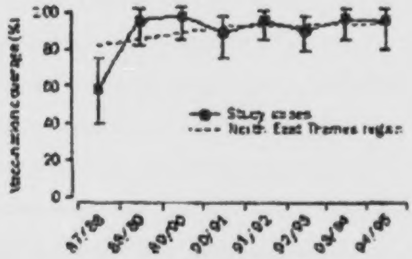

Figure 2: MMR vaccine coverage by second birthday and year of birth

Error bars=95% CI. Coverage figures for birth cohorts in North East Thames obtained from Vaccination and Immunisation Summary Information for 1996–97 produced by Government Statistics Service DH Statistics Division.

Event and risk period (months)	MMR vaccine(s)		MMR, measles, mumps and rubella vaccine(s)	
	Relative incidence (95% CI)	Number of events	Relative incidence (95% CI)	Number of events
Autism diagnosis (n=357)				
<12	0·94 (0·60–1·47)	31	0·80 (0·53–1·22)	36
<24	1·09 (0·79–1·52)	138	1·05 (0·78–1·44)	182
Parental concern (n=326)				
<6	1·48 (1·04–2·12)	75	1·19 (0·84–1·69)	82
<12	0·90 (0·63–1·29)	120	0·86 (0·60–1·23)	142
Regression (n=165)				
<2	0·92 (0·38–2·21)	7	1·24 (0·60–2·56)	11
<4	1·00 (0·52–1·95)	17	1·31 (0·73–2·33)	24
<6	0·85 (0·45–1·60)	23	0·99 (0·56–1·75)	35

Table 2: Relative incidence and numbers of events in risk periods after vaccination with one or more MMR vaccine or one or more MMR, single-antigen measles and mumps plus rubella vaccines, by event type in children with core or atypical autism

at diagnosis, these cases were not included in further analyses of vaccination status.

Of the 356 cases of core or atypical autism with age at diagnosis of 18 months or greater, 233 received MMR vaccine before this age, 64 never received MMR vaccine, and 59 received MMR vaccine at 18 months or later. There were no differences in age at diagnosis between those vaccinated before or after 18 months of age and those never vaccinated (p=0·41) and no interaction between these vaccine categories and year of birth (p=0·29). The parameter estimates, expressed as fold-differences in geometric mean ages were: vaccinated before 18 months over unvaccinated 0·91 (95% CI 0·79–1·05); vaccinated after 18 months over unvaccinated 0·93 (0·81–1·08).

The results of the case-series analyses are shown in table 2; the results were similar when the analysis was restricted to cases confirmed by ICD10 criteria. There was no significant clustering of interval to diagnosis or regression within the time periods defined. There was a significant clustering of parental concern within 6 months of vaccination (p=0·03) but no significant excess risk in any of the other periods investigated (<1, <2, <3, <4, <5, <7, <8, <9, <10, <11, and <12 months after vaccination). The distribution of parental concern by interval in months since latest MMR vaccination showed a peak at 5 months (22 cases compared with a range of four to 14 for the remaining intervals up to 12 months). This excess was largely attributable to the peak recorded age of parental concern being 18 months, combined with the peak in MMR vaccination at 13 months. When the data were reanalysed without cases with recorded age at parental concern of 18 months (n=61), all statistical significance disappeared. For case-series analyses restricted to cases of core autism, the results (not shown) were similar to those in table 2 with the exception of age at onset of parental concern within 6 months of MMR vaccination, which showed no significant excess risk (relative incidence 1·25 [95% CI 0·81–1·95]); the relative incidence for atypical cases when analysed separately remained raised at 1·99 (1·08–3·68).

Discussion

Vaccination and vaccine safety are issues of major concern to the public, their elected representatives, and all health-care workers. Possible adverse reactions to vaccines have a particular attraction to various pressure groups and to the media, with important, and possibly catastrophic, effects on public confidence in immunisations and on vaccine uptake.[16] The study by Wakefield and others[1] and earlier work from those investigators suggesting an association between measles-containing vaccines and inflammatory bowel disease[11,13] (not confirmed in their subsequent studies[15-17]) received much media attention and have had an adverse effect on immunisation uptake.[18] The consequences of these events are that many children are now at risk of measles, mumps, and rubella, and that the possibility of eradication of measles has been delayed.

Our study was designed to test the hypothesis that MMR vaccination is causally associated with autism. The study has some limitations: two of these are that we could not verify the diagnosis according to ICD10 criteria in some cases, and that the ascertainment may have been incomplete. The clinical notes were of variable quality and many did not contain systematic or regularly updated information which would have allowed independent validation of the diagnosis, particularly in the children with atypical autism or Asperger's syndrome. However, we have confidence in the overall reliability of the diagnosis of autism in our study. Most cases were documented as having been assessed by specialist clinicians, and the remainder are highly likely to have been as well. There was close similarity between the ICD10-confirmed and non-confirmed cases, and all the analyses showed almost identical results when repeated with only ICD10-confirmed cases. We made substantial efforts to capture all cases of autism in study districts from multiple sources, but inevitably some cases will have been missed, particularly children educated outside their borough and not known to local health services or education authorities. Nevertheless, our prevalence rates for autism are similar to those reported in other contemporary studies.[19] Incomplete case ascertainment would not affect the validity of our results for the case-series analyses unless the unidentified children with autism were more likely than those we identified to have had onset in close temporal association with MMR vaccine; this possibility seems unlikely.

There is uncertainty about whether the prevalence of autism is increasing.[20] Our study is consistent with an increase in the incidence of autism in recent birth cohorts. This increase may be real or a reflection of other factors such as better recording arrangements in recent years, the increasing recognition of higher functioning children with autism and Asperger's syndrome, together with an increasing number of professionals trained to recognise the disorders. However, whether real or artifactual, the trend in increasing incidence with successive birth cohorts to 1992 was not related to the introduction of MMR vaccine or to vaccine coverage, which reached a plateau during a period in which autism incidence was apparently increasing.

We looked for evidence of a possible causal association between MMR vaccination and onset of autism by investigating whether, after adjustment for birth-cohort effects on incidence, age at diagnosis of autism varied with vaccination status. The age at diagnosis was found to be independent of whether MMR vaccine was given, or in those vaccinated, whether the vaccine was given before or after 18 months of age—the earliest age at diagnosis of core or atypical autism. The proportion of

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core and atypical cases vaccinated by the end of the second year of life was similar to that in the same birth cohorts in the North East Thames region. None of these analyses suggest a causal association between MMR vaccination and autism.

The case-series analyses showed no evidence of temporal clustering between MMR or other measles-containing vaccines and diagnosis of autism. Regression, as reported in other studies,[1] occurred in nearly a third of the cases of core autism; regression was not clustered in the months after vaccination. For age at first parental concern, no significant temporal clustering was seen for cases of core autism or atypical autism, with the exception of a single interval within 6 months of MMR vaccine associated with a peak in reported age at first parental concern at 18 months. This peak is likely to reflect the difficulty experienced by parents in defining the precise age at onset of symptoms in their child, particularly those with atypical autism, and consequent approximation with preference for 18 months.

Our results do not support the hypothesis that MMR vaccination is causally related to autism, either its initiation or to the onset of regression—the main symptom mentioned in the paper by Wakefield and others.[1] The data on clinical presentation and immunisation status of the cases in our study were recorded before the recent publicity suggesting a possible link between MMR vaccine and autism. The two data-sets were collected independently of each other, so avoiding the bias that can occur when cases are ascertained as a result of a perceived link with vaccination. This study does not rule out the possibility of a rare idiosyncratic response to MMR. However, if such an association occurs, it is so rare that it could not be identified in this large regional sample. Our findings, based on a large study, confirm and extend those of Gillberg and Heijbel,[19] which showed no evidence of a causal association between MMR vaccine and autistic disorder in Sweden. We hope our results will reassure parents and others who have been concerned about the possibility that MMR vaccine is likely to cause autism and that they will help restore confidence in MMR vaccine.

Contributors

Brent Taylor, Elizabeth Miller, Christina Petropoulos, and Jun Li were responsible for study design. Brent Taylor, Christina Petropoulos, and Isabelle Favot-Mayaud were responsible for case identification and ascertainment. Paddy Farrington undertook the statistical analyses. Elizabeth Miller, Pauline Waight, Jun Li, Isabelle Favot-Mayaud, and Brent Taylor were responsible for data handling and processing. All investigators contributed to the writing of the paper.

Acknowledgments

We thank Nick Andrews (CDSC) for his help with statistical analysis, Andrew Lloyd Evans (neurodevelopmental paediatrician) and Sarah Willenberg (speech therapist) for advice, and Ioanna Konstagianni and Ekundayo Ajani-Obe for help with piloting and data collection. The study was funded by the Medicines Control Agency.

References

1 Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998; 351: 637–41.
2 Chen RT, DeStefano F. Vaccine adverse events: causal or coincidental? *Lancet* 1998; 351: 611–12.
3 Lee JW, Melgaard B, Clements CJ, Kane M, Mulholland EK, Olivé J-M. Autism, inflammatory bowel disease, and MMR vaccine. *Lancet* 1998; 351: 905.
4 Bedford H, Booy R, Dunn D, et al. Autism, inflammatory bowel disease, and MMR vaccine. *Lancet* 1998; 351: 907.
5 Siegel B, Pliner C, Eschler J, Elliot G. How children with autism are diagnosed: difficulties in identification of children with multiple developmental delays. *J Dev Behav Paediatr* 1988; 9: 199–204.
6 Nicholl A, Elliman D, Ross E. MMR vaccination and autism 1998. *BMJ* 1998; 316: 715–16.
7 Farrington CP. Relative incidence estimation from case series for vaccine safety evaluation. *Biometrics* 1995; 51: 228–35.
8 Farrington CP, Nash J, Miller E. Case series analysis of adverse reactions to vaccines: a comparative evaluation. *Am J Epidemiol* 1996; 143: 1165–73.
9 Farrington P, Pugh S, Colville A, et al. A new method for active surveillance of diphtheria/tetanus/pertussis and measles/mumps/rubella vaccines. *Lancet* 1995; 345: 567–69.
10 Gangarosa EJ, Galazka AM, Wolfe CR, et al. Impact of anti-vaccine movements on pertussis control. the untold story. *Lancet* 1998; 351: 356–61.
11 Wakefield AJ, Pittilo RM, Sim R, et al. Evidence of persistent measles virus infection in Crohn's disease. *J Med Virol* 1993; 39: 345–53.
12 Thompson NP, Montgomery SM, Pounder RE, Wakefield AJ. Is measles vaccination a risk for inflammatory bowel disease? *Lancet* 1995; 345: 1071–74.
13 Thompson NP, Pounder RE, Wakefield AJ. Perinatal and childhood risk factors for inflammatory bowel disease: a case control study. *Eur J Gastroenterol Hepatol* 1995; 7: 385–90.
14 Morris DL, Montgomery SM, Ebrahim S, Pounder RE, Wakefield AJ. Measles vaccination and inflammatory bowel disease in the 1970 British cohort study. *Gut* 1997; 41 (suppl 3): 37 (abstr).
15 Chadwick N, Bruce IJ, Schepelmann S, Pounder RE, Wakefield AJ. Measles virus RNA is not detected in inflammatory bowel disease using hybrid capture and reverse transcriptase followed by polymerase chain reaction. *J Med Virol* 1998; 55: 305–11.
16 CDSC. COVER/Korner: April to June 1998. *Commun Dis Rep CDR Wkly* 1998; 8: 345–46.
17 Fombonne E, D Mazaubrun C, Cans C, Grandjean H. Autism and associated medical disorders in a large French epidemiological sample. *Am Acad Child Adolesc Psychiatry* 1997; 36: 1561–69.
18 Wing L. Autistic spectrum disorders: no evidence for or against an increase in prevalence. *BMJ* 1996; 312: 327–28.
19 Gillberg C, Heijbel H. MMR and autism. *Autism* 1998; 2: 423–24.

thromboses, five extra endometrial cancers, and no extra deaths. Counterbalancing these side-effects were 29 fewer invasive breast cancers and 17 fewer in-situ carcinomas. For every 19 women treated with tamoxifen, one event was avoided. Over half of all ipsilateral recurrences were treated with mastectomy. By extrapolation from the data presented, 22 mastectomies were prevented by tamoxifen, with one mastectomy avoided for every 40 women treated.

From a biological standpoint, ER function and expression are fascinating and of direct relevance to primary prevention as well as to treatment of DCIS. ER expression is not routinely tested for in DCIS, but perhaps it should be now. Data cited by Fisber and colleagues show that ER-positivity rates in DCIS are high, although less so where comedonecrosis is present.[5] Parallels with NSABP P-1 come to mind, since in that prevention trial, tamoxifen seems to have delayed or prevented ER-positive cancers preferentially. If this finding were to apply in DCIS as well, it would strengthen the notion that ER expression (and subsequent phenotypic behaviour) is an early event in the development of breast cancer. Since not all DCIS is ER positive, this disorder might be a good model for targeting non-ER-mediated molecular pathways in the search for new preventive and therapeutic strategies.

Where to now? The next generation of studies needs to refine the outstanding achievements of NSABP B-17 and B-24. Specifically, information is needed on whether a defined group of women with DCIS can be treated with breast-conserving surgery alone, and whether another group can be treated with surgery and radiotherapy but without tamoxifen. For now, putting it all together is a matter for negotiation between patient and clinician. A reasonable view of the data presented should be that the benefits of tamoxifen far outweigh the risks. Should all women with mammographically detected DCIS have tamoxifen? Probably no. Should most? Probably yes.

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1 Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomised trials. *Lancet* 1998; 351: 1451–67.

2 Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst* 1998; 90: 1371–88.

3 Fisher B, Dignam J, Wolmark N, et al. Lumpectomy and radiotherapy for the treatment of intraductal breast cancer: findings from the National Surgical Adjuvant Breast and Bowel Project B-17. *J Clin Oncol* 1998; 16: 441–52.

4 Silverstein MJ, Lagios MD, Groshen S, et al. The influence of margin width on local control of ductal carcinoma in situ of the breast. *N Engl J Med* 1999; 340: 1455–61.

5 Barnes R, Masood S. Potential value of hormone receptor assay in carcinoma in situ of the breast. *Am J Clin Pathol* 1990; 94: 533–37.

Negative association between MMR and autism

See page 2026

Early last year we cautioned[1] against premature acceptance of a hypothesis, proposed in a reported case-series, that measles, mump, and rubella (MMR) vaccination may cause autism, possibly by a mechanism involving induction of bowel abnormalities.[2] We were especially concerned that the reported cases may have been due simply to temporal coincidence, and by the lack of supportive laboratory evidence. A special panel of the UK Medical Research Council also found the evidence unconvincing.[3] Nonetheless, the hypothesis generated much media attention in the UK, with a subsequent drop in acceptance of MMR vaccinations.[4]

Less noticed were reports by the same group (and others) that highly specific laboratory assays in patients with inflammatory bowel disease (IBD), the postulated mechanism for autism after MMR vaccination, were negative for measles virus.[5,6] This week sees the publication of two other reports that do not support a causal association between MMR (or other measles-containing vaccines) and autism or IBD. One report is by the Working Party on MMR Vaccine of the UK's Committee on Safety of Medicines.[7] The Working Party was charged with the evaluation of several hundred reports, collected by a firm of solicitors, of autism, Crohn's disease, or similar disorders developing after MMR or MR vaccination. The Working Party conducted a systematic, standardised review of information from parents and physicians. Although acknowledging that it is impossible to prove or refute the suggested associations (because of variable quality of data, biased selection of cases, and lack of a control group), the Working Party concluded that the information available did not support the suggested causal associations or give cause for concern about the safety of MMR or MR vaccines.

In today's *Lancet*, Brent Taylor and colleagues provide population-based evidence that overcomes many of the limitations faced by the Working Party. Taylor and colleagues identified all 498 known patients with autism spectrum disorders (ASD) in North East Thames who had been born in 1979 or later, and linked them to an independent regional vaccination registry. ASD includes typical (core) autism, atypical autism, and Asperger's syndrome, but the results were similar when cases of core autism were analysed separately. The investigators first showed that the known number of cases of ASD cases has been increasing since 1979 and that there was no sharp increase after the introduction of MMR vaccine in 1988. Second, they found that, among affected individuals, the age at diagnosis was similar whether the child had been vaccinated before or after age 18 months, or had not been vaccinated, which indicates that vaccination does not result in earlier expression of autistic characteristics. Third, they showed that at age 2 years MMR vaccination coverage among the children with ASD was nearly identical with that in children in the same birth cohorts in the whole region, which provides evidence of an overall lack of association with vaccination.

Taylor and colleagues then used an innovative "case-series" method to assess the relative incidence of autism within predefined time periods after vaccination. These analyses involved three different measures of onset of autism (date of diagnosis, date of first parental concern, and date of regression) and two vaccine categories (MMR and any measles-containing vaccine). No statistically significant associations were found in the 14 comparisons, except for a slightly increased relative incidence (1·48) for the association of MMR vaccination and initial parental concern (which seems to have been due to parents' difficulty in recalling the precise age at onset and hence a preference for approximating the age as 18 months). Although the case-series method may be better suited for the study of an acute disease than of chronic disorders with an insidious onset, such as ASD, the results are buttressed by the lack of associations found in the other analyses.

The findings also are consistent with current understanding of the pathogenesis of autism, a syndrome defined by certain behavioural and developmental characteristics that may have a variety of causes. In few cases, however, is a specific cause identified. Autism has a strong genetic component, and associated neurological defects probably occur early in embryonic development.[8] Thus, in most cases, autism represents a birth defect, although it may not be diagnosed until later in life when communication delays and characteristic behaviours become apparent. It seems unlikely therefore that a vaccination that is given after birth could cause autism.

Rare cases have, however, been described, of a normal child regressing and acquiring autistic characteristics. It is such cases of regressive disorders for which a biological link with vaccination is plausible.[8] The onset of developmental regression tends to be clearly demarcated, making the disorder more amenable to the case-series method. Thus, Taylor and colleagues' analysis showing no association between vaccination and onset of regression provides especially persuasive evidence against the hypothesis that MMR may cause or exacerbate autism.

Taylor and colleagues conclude with the hope that their results "... will reassure parents and others who have been concerned about the possibility that MMR vaccine is likely to cause autism and that they will help restore confidence in MMR vaccine". Will the scientifically sound but essentially "negative" results published this week garner the same media and public attention as the initial report of the MMR-autism hypothesis? It is unlikely, as evidenced by the renewed media frenzy last week in response to another report by the group that proposed the hypothesis. This report was of an increased risk of IBD among individuals who had naturally acquired measles and mumps within 1 year of each other.[9] The study had no data on MMR vaccine and the investigators specifically stated that they did not find a significant relation between monovalent measles vaccination alone and later IBD. Yet the popular media trumpeted the study as providing evidence that MMR vaccination may cause IBD. In such an environment it is critical to strengthen vaccine safety monitoring systems and risk-communication strategies to maintain public confidence in immunisations.

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1 Chen RT, DeStefano F. Vaccine adverse events: causal or coincidental? *Lancet* 1998; 351: 611–12.
2 Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998; 351: 637–41.
3 Bignall J. UK experts convinced of safety of MMR. *Lancet* 1998; 351: 966.
4 Thomas D Rh, Salmon RL, King J. Rates of first measles-mumps-rubella immunisation in Wales (UK). *Lancet* 1998; 351: 1927.
5 Chadwick N, Bruce IJ, Schepelmann S, Pounder RE, Wakefield AJ. Measles virus RNA is not detected in inflammatory bowel disease using hybrid capture and reverse transcription followed by polymerase chain reaction. *J Med Virol* 1998; 55: 305–11.
6 Duclos P, Ward BJ. Measles vaccines: a review of adverse events. *Drug Safety* 1998; 19: 435–54.
7 Medicines Control Agency/Committee on Safety of Medicines. The safety of MMR vaccine. *Curr Probl Curr Pharmacovigilance* 1999; 25: 9–10.
8 Rodier PM, Hyman SL. Early environmental factors in autism. *MRDD Res Rev* 1998; 4: 121–28.
Montgomery SM, Morris DL, Pounder RE, Wakefield AJ. Paramyxovirus infections in childhood and subsequent inflammatory bowel disease. *Gastroenterology* 1999; 116: 796–803.

Benefit of β-blockers for heart failure: proven in 1999

See page 2001

The rationale for β-blocker use in heart failure, based on neurohormonal physiology, has been established over the past 20 years. Now, a little more than 10 years after publication of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS),[1] which first indicated the survival benefit of inhibition of angiotensin-converting enzyme (ACE) in severe heart failure, the additional benefit of β-blockade is also well proven. With the publication today of the mortality results of the Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF) by the Göteborg group who pioneered this approach, there are now sufficient data to indicate certainty of benefit and to provide a basis for recommending β-blocker use in appropriate patients.

Between 1980 and 1997, 24 randomised controlled trials of β-blockers in heart failure were reported.[2,3] These trials included a total of 3141 patients with ischaemic or non-ischaemic causes of heart failure; more than 80% were on standard ACE-inhibitor treatment. A few trials accounted for most of the patients: the Metoprolol in Dilated Cardiomyopathy (MDC) study,[4] the Cardiac Insufficiency Bisoprolol Study (CIBIS),[5] and the Australia and New Zealand[6] and US carvedilol[7] trials. More than half the patients were included in trials of non-selective agents, of which carvedilol was the most commonly used. Overall, the effects on symptoms and exercise tolerance varied, but left-ventricular function was consistently improved.[2] Hospital admissions were reduced in the larger studies, and a meta-analysis[3] showed a 31% reduction in mortality with β-blockers (odds ratio 0·69 [95% CI 0·54–0·89], 2p=0·0035), the mean annual mortality being reduced from 9·7% to 7·5%.

This year has seen the publication of two adequately powered studies, CIBIS-II[8] and MERIT-HF, the results of which are consistent with each other and also almost exactly superimpose on the findings of the previous meta-analysis. MERIT-HF is the largest trial so far. It included 3991 patients with heart failure in New York Heart Association functional class II–IV and with left-ventricular ejection fraction of under 40%, on standard therapy. Treatment with long-acting metoprolol conferred a 34% reduction in mortality (relative risk 0·66 [0·53–0·81]), annual mortality being reduced from 11·0% to 7·2%. There were significant reductions in both sudden deaths and deaths due to worsening heart failure. From the results, 27 patients have to be treated for 1 year to prevent one death, which indicates unusually high cost-effectiveness.

ACE inhibition in heart failure improves symptoms, haemodynamics, ventricular remodelling, and survival. The survival benefit from an overview of controlled trial data (32 trials in 7105 patients) ranges from 12% to 33%,[9] and it is due primarily to a reduction in deaths from worsening heart failure, but there is no clear evidence of a reduction in sudden death. The effect of β-blockade seems additive to that of ACE inhibition. In both CIBIS-II and MERIT-HF, sudden deaths were significantly reduced. Deaths from progressive heart failure were significantly reduced in MERIT-HF and showed a trend to reduction in CIBIS-II. In MERIT-HF, sudden death was more common with less severe heart failure. Overall, this

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Correspondence Volume 355, Number 9201 · 29 January 2000

Previous · · Next

Autism and measles, mumps, and rubella vaccine

Lancet 2000; 355: 409 - 414 Download PDF (609 Kb)

Sir--The paper by Brent Taylor and colleagues [1] will reassure the general public that there is no substantial association between measles, mumps, and rubella (MMR) vaccination and autism. However, I would like to know a little more detail about the first two analyses in the study.

For their first analysis, Taylor and colleagues state in the Summary that "there was a steady increase in cases by year of birth with no sudden 'step-up' or change in the trend line after the introduction of MMR vaccination". The visual support for this statement is given in their figure 1, which apparently shows cases increasing before the introduction of the vaccine to the 1987 birth cohorts, the "first birth cohorts eligible for MMR vaccine in the second year of life"; and the statement is supported statistically by a non-significant test for a "step-up" at this time point. The persuasiveness of the graph and the choice of this time point rest presumably on the idea that cases born before 1987 either would not have been vaccinated or would have been vaccinated after they were diagnosed as having autism. But children born before 1987 were also eligible for MMR vaccination, albeit after their second year of life. I have not been able to deduce from the numbers presented how many of the 109 study children born before 1987 received MMR vaccine. Could Taylor and colleagues supply the relevant details of this group of 109 (in particular the number vaccinated before diagnosis)? They could also helpfully give some idea of the proportion of the population vaccinated by year of birth, starting at the 1983 birth cohort, the earliest which in principle could have been vaccinated before a diagnosis under age 60 months. Readers could then assess whether a single "step-up" or a more gradual increase should be expected if there were a causal association.

As regards the second analysis, there are two issues on which further clarification is desirable. Taylor and colleagues found that age at diagnosis did not differ between the three groups (children vaccinated before 18 months, at or after 18 months, or never vaccinated). However, this finding is useful only if age at diagnosis is closely related to the true age of onset of symptoms. There is some evidence that this may not be the case. Research by the National Autistic Society found that 40% of parents wait more than 3 years for a diagnosis.[2] Indeed, Taylor and colleagues allude to delays in diagnosis. There is therefore some need for caution in interpretation here. Although the variable age at parental concern is heavily prone to bias, use of age at diagnosis in this context may introduce an important bias in the opposite direction (ie, towards obtaining a negative finding).

An equivalent analysis with age at parental concern, which showed no evidence of a difference between the three groups, would be particularly reassuring, because it would be despite a bias working towards a positive finding.

Secondly, because Taylor and colleagues presented evidence for an absence of association, regression coefficients and CIs would be helpful, rather than just the p value (0·41) for what I guess is the *F* test for the null hypothesis of no difference in the (geometric) means of the three groups. In the absence of explicit power calculations, I would like to know that any differences in means were small as well as non-significant.

I am surprised that so much of the burden of public reassurance is made to fall on attempts to show that there is no association between autism and MMR vaccination. I have been persuaded to have my own child vaccinated mainly by the fundamental idea that the risks from not vaccinating are substantially higher than those from vaccinating. What I would find helpful is a calculation of how many cases of autism would have to be caused by MMR--if there were a causal association--for the risks of vaccinating to outweigh the risks of not vaccinating.

Dan Altmann

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1 Taylor B, Miller E, Farrington CP, et al. Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association. Lancet 1999; 353: 2026-29.

2 Stirling A, Prior A. Opening the door. London: National Autistic Society, 1999.

Authors' reply

Sir--Dan Altmann is correct in noting that some children born before 1987 received MMR vaccine. This issue was raised by Wakefield .[1] We responded[2] by identifying the 36 children in our cohort born before 1987 who received MMR vaccine. Age at parental concern was recorded in 29 of these; in all cases this was before MMR vaccination was given. Thus the "catch-up" programme could have had no effect on our findings. Nor do these findings support Wakefield's assertion[1] that the apparent rise in the prevalence of autism up to 1992 can be linked to the introduction of MMR vaccine.

We agree with Altmann that there may be delay in the diagnosis of autism. He suggests that such delays might have affected the power of our analyses on age at diagnosis by vaccine group. We presented that analysis in our paper, with parameter estimates and CIs as well as p values. We have undertaken a further analysis, as Altmann suggests, of age at parental concern by vaccine group; this presented some difficulties because parental concern predated vaccination in many more cases than did age at diagnosis. We restricted the analysis to the 244 cases with age at parental concern between 15 months and 48 months (excluding two unvaccinated outliers with first parental concern at 84 months and 132 months). We found no significant difference in mean log age at parental concern between children receiving MMR vaccine before the age of 15 months (n=108), those receiving vaccine at 15 months or later (n=88), and those not receiving MMR vaccine (n=48). The p value for the *F* test was 0·61 and the parameter estimates, expressed as fold-differences in geometric mean ages, were: vaccinated before 15 months over unvaccinated 0·96 (95% CI 0·86-1·09); vaccinated after 15 months over unvaccinated 0·94 (0·84-1·06). Similar results were obtained (p=0·35) for the 229 cases with age at parental concern at 18 months or later, with vaccine recipients categorised into those receiving MMR vaccine before or after age 18 months.

We agree with Altmann that the benefits of vaccination outweigh the risks. The purpose of our study was to address a specific hypothesis on a possible association between MMR vaccination and autism raised by Wakefield and colleagues.[3] These investigators were careful to emphasise that they had not proved such an association. The three senior paediatricians involved subsequently emphatically endorsed current vaccination policy.[4] The negative findings of our study reinforce these messages.

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1 Wakefield AJ. MMR vaccination and autism. *Lancet* 1999; 354: 350.

2 Taylor B, Miller E, Farrington P. MMR vaccination and autism. *Lancet* 1999; **354:** 350.

3 Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998; 351: 637-41.

4 Murch S, Thomson M, Walker-Smith J. Autism, inflammatory bowel disease, and MMR vaccine. *Lancet* 1998; 351: 908 [PubMed].

Previous ‹ › Next

what's new? Medical Research Council MRC

REF: MRC/18/00

ISSUED: Monday 3 April 2000

NO NEW EVIDENCE OF A LINK BETWEEN MMR AND AUTISM

New Research Will Study The Possible Causes Of Autism

An expert group of scientists and doctors, brought together by the Medical Research Council (MRC), today (Monday 3 April 2000) published a report which concludes that there is no new evidence to suggest a causal link between MMR (measles, mumps, rubella) vaccination and autism or inflammatory bowel disorders (IBD).

The group was set up following an ad hoc meeting of experts in March 1998 to steer and monitor research into inflammatory bowel disorders and autism. The group's main conclusions are:

- Between March 1998 and September 1999 there was no new evidence to suggest a causal link between MMR and IBD/autism (confirming the earlier view of the ad hoc group)
- Much remains unknown about inflammatory bowel disorders and autism and more research in these areas is needed

The group was chaired by Professor Alan McGregor of the GKT School of Medicine at King's College, London. The report is published on the MRC's web site at www.mrc.ac.uk/Autism_report.html

The MRC also announced today that it is to fund one of the largest studies of autism ever attempted. The study, to be led by Professor Andrew Hall of the London School of Hygiene and Tropical Medicine, will attempt to find out what causes the condition.

The researchers will study whether autistic children have a history of other conditions or medical problems, for example, problems during birth. They will look at whether viral infections in the womb or soon after birth appear to play a role in producing autism. By looking at a representative sample of health records drawn from over two million people registered with 300 general practices across the UK, the researchers will also be able to examine any possible association between autism and the MMR vaccine.

Professor Hall said: "Partly because of its rarity, we know very little about what causes autism. Most of the studies to date have been small and have not considered all the possible risk factors simultaneously. We hope our study will begin to answer some of the questions about this important developmental disorder."

The study is one of 85 new grants totalling almost £44 million announced by the

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MRC to fund scientific research programmes in many areas of health and medicine. MRC's total support for medical research in the 1999-2000 financial year is approximately £331 million.

For more information contact the MRC press office on 020 7637 6011.

NOTES TO EDITORS

The Medical Research Council (MRC) established in 1913, aims to improve health by promoting research into all areas of medical and related science. It is funded mainly by the government, but is independent in its choice of which research to support. About half of the MRC's expenditure of £315.9 million is invested in over 50 of its Institutes and Units, where it employs its own research staff. The remaining half goes in the form of grant support and training awards to individuals and teams in universities and medical schools

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Top of page | Top of section | Homepage

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REPORT OF THE STRATEGY DEVELOPMENT GROUP SUBGROUP ON RESEARCH INTO INFLAMMATORY BOWEL DISORDERS AND AUTISM

1. Background

In March 1998, the MRC had held an *ad hoc* meeting of experts to examine evidence relating measles vaccine to chronic gastrointestinal inflammation. The main conclusions of this meeting had been that:

i. the balance of available virological and epidemiological evidence was against the persistence of measles in Crohn's disease;
ii. there was no correlation between measles or mumps infection alone and Crohn's Disease or ulcerative colitis (UC); and
iii. there was no current evidence linking bowel disease or autism with MMR vaccine and there was thus no reason, arising from the work considered, for a change in the current MMR vaccination policy.

Following this meeting, Council had decided to set up an Expert Subgroup (as a Subgroup of the Strategy Development Group) to steer and monitor research in these areas.

6. Conclusions & recommendations

6.1. Conclusions

Based on their discussions during the four meetings, the main conclusions of the Subgroup were that:

i. much remained unknown about inflammatory bowel disorders and autism
ii. MRC support for research in these areas, and IBD in particular, was relatively weak
iii. between March 1998 and September 1999 there had been no new evidence to suggest a causal link between MMR and IBD/autism, (confirming the earlier view of the *ad hoc* Group).

6.2 Recommendations

6.2.1 Research

In the course of discussion of current and future research strategies, the Subgroup identified a number of areas of study that might serve to elucidate the aetiology and pathogenesis of IBD and autism, and to evaluate treatments or management approaches.

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i) Inflammatory bowel disorders

- Investigation of childhood risk factors; large-scale multi-centre/international epidemiological studies – case-control studies or extensive prospective studies involving epidemiologists, professional bodies, charities
- Investigation of extrinsic environmental factors (smoking, prescription drugs) as possible factors in the development or progression of IBD
- Independent studies to replicate and/or further explore the alleged association between paramyxovirus infection in childhood and subsequent inflammatory bowel disease
- Genetic studies (physical mapping of chromosomes 12 and 16, further investigation of candidate genes, identification of predictive factors, population (including migration) studies)
- Basic studies on the role of microbiological flora and the immune response to them
- Investigation of the role of infections and use of antibiotics
- Cytokine studies (including animal gene 'knock-out' experiments and investigating the influence of microbiological challenge on the gut cytokine networks)
- Multi-centre/international trials of new treatments (anti-sense/anti-cytokine antibodies)

ii) Autistic spectrum disorders

- Investigation of childhood risk factors; large-scale multi-centre/international epidemiological studies - case control studies or extensive prospective studies involving epidemiologists, professional bodies, charities and parents
- Well-controlled epidemiological studies concentrating on all late-onset cases (whatever the cause) and characterising them in contrast with those of early origin (with the collaboration of parents)
- Life course studies on adult patients
- Phenotype characterisation
- Search for biological markers of autism
- Independent multicentre prospective controlled study of bowel function in autistic children to establish whether "autistic enterocolitis" is a real syndrome
- Development of reliable non-invasive tests for IBD to facilitate independent investigation of incidence of gastrointestinal involvement in autism
- Consideration of the possibility of multi-centre clinical trials of drug treatments in well-defined groups
- Study to determine the prevalence and possible biological /functional significance of autoantibodies (particularly anti-brain antibodies) in children with autism

iii) Generic research issues

- That any future epidemiological studies (case-control or prospective) in IBD and autism should use similar tools to generate the epidemiological data
- The use of mathematical modelling to look at linkage of immunisation with idiosyncratic events
- Investigation of long-term consequences of immunisation, in general
- Involvement of parents of autistic children and patient/special interest groups in the planning and monitoring of future trials and studies

6.2.2 Training

- Specialist training, particularly in mucosal immunology (available in the USA)

6.2.3 Other areas

- Improved collaboration between clinicians
- Identification of services required by patients, particularly nursing services
- Improved means of communication of science to the media and general public

7. Suggestions for future work of the Subgroup

a. To advise on outline proposals submitted to the Office in response to any MRC initiatives
b. To respond to enquiries and correspondence from the public and other sources, as appropriate
c. To keep a watching brief and review any reports of a purported link between MMR immunisation, IBD and autism
d. To explore other aspects of IBD and autism

Source: The Times (Early Edition)
Date: Tuesday 17th August 1999
Page: 1 - 2
Circulation: 751862 Daily

Doctors fear measles epidemic by 2001

By IAN MURRAY
MEDICAL CORRESPONDENT

A MEASLES epidemic early in the next millennium is all but inevitable, doctors said yesterday, as new figures showed that immunisation rates against the disease among babies are dangerously low.

The figures are causing such alarm that doctors are beginning to ask whether vaccination should be made compulsory.

Only 87 per cent of babies are now being given the triple measles, mumps and rubella jab by the recommended age of 15 months, against the 95 per cent needed to keep immunity levels high enough to prevent an epidemic.

"If there is [illegible] Mary Ramsay, of the Public Health Laboratory Service, said, although [illegible] specialist speculates today that while compulsory vaccination cannot be justified at the moment there might come a time when it would be necessary in the public interest. "If the level of population immunity were to fall for a particular vaccine preventable infectious disease, compulsory vaccination might become a morally justifiable option," Peter Bradley, specialist registrar in public health medicine at the North Staffordshire Health Authority, writes in the *Journal of Medical Ethics*.

Vaccination rates have been falling since February last

Continued on page 2, col 5

Fear of measles epidemic in 2001

Continued from page 1

year, when a report implied a possible link between the MMR vaccine and autism, in spite of eminent experts "discounting the danger and government attempts to reassure parents.

"There is a lack of knowledge in the community about the risks and benefits of vaccination against a particular disease," Dr Bradley said. "A minority can put the whole community at risk by refusing vaccination, and society as a whole has to question whether their objections are justified."

Immunisation programmes have made measles rare in developed countries, but it remains the world's sixth most deadly infectious disease and about one child in a thousand who catches it will either die or suffer brain damage.

Noel Olsen, a senior member of the British Medical Association's public health committee, said there was some sympathy with systems in America and France which make vaccination virtually compulsory. In America children do not have to be vaccinated but they cannot go to school until they are and parents are prosecuted if they do not send their children to school. In France child welfare payments are available only to parents of vaccinated children.

The Health Department said that it had no plans to make vaccination compulsory and was relying on better education through GPs. Immunisation against infectious diseases was made compulsory in the middle of the 19th century but proved unpopular and the law was repealed in 1948.

742

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↓ EXPAND STORY

American Academy of Pediatrics Says Evidence Confirms No Link . Between Autism and Vaccines

To: National Desk, Health Reporter Contact: Marjorie Tharp or Sherry Llewellyn, 202-347-8600, both of the American Academy of Pediatrics; Web site: http://www.aap.org

WASHINGTON, April 6 /U.S. Newswire/ -- In response to a U.S. House Government Reform Committee hearing today, the American Academy of Pediatrics wants to reassure parents that vaccines are the safest way to protect children against potentially devastating infectious diseases.

"What a tragedy it would be for any child to suffer the consequences of a disease that could have been prevented by vaccination," AAP President Donald Cook, M.D., said.

If parents refuse to immunize their children, this country will see a resurgence of epidemics of these diseases. The measles epidemic of 1989-1991 in this country affected more than 55,000 people; 11,000 were hospitalized and more than 120 died. A major cause of the epidemic was failure to vaccinate children on time at 12-15 months of age.

The congressional hearing is focusing on autism, including an unsubstantiated link to vaccines such as MMR (measles, mumps and rubella).

"While I support any effort to discover the reason a child has autism, current scientific data indicate that vaccines are not the cause," Dr. Cook said.

Autism manifests itself in the first three years of life, which is the same time a child is being vaccinated, but timing is the only link. A study in the British medical journal Lancet found similar autism rates among children who received the MMR vaccine and those who had not. A report commissioned by Britain's Medical Research Council and released this week found that there was no link between MMR and autism or bowel disorders.

The American Academy of Pediatrics supports aggressive research into the causes, treatment and prevention of autism as many questions remain. The perceived increase in autism cases could be attributed to a number of factors, and additional study is needed.

Vaccines are developed through rigorous research designed to ensure safe and effective products. These products are then subjected to another level of intense scrutiny in order to assure that recommendations about immunization practices and procedures reflect the best available science. Once approved for use, there is a robust system of checks and balances that monitors the safety and efficacy of vaccines.

A child's chance of being harmed by an infectious disease like measles or mumps is far greater than any risk of being harmed by the vaccine. These diseases have not been eliminated, only kept at bay through widespread childhood immunization. Measles, for example, can lead to pneumonia or an infection of the brain and can cause death. Mumps can cause an infection in the lining of the brain and death.

To help inform parents about the benefits and risks of vaccines, the American Academy of Pediatrics has developed brochures that are distributed by pediatricians. Vaccine information can also be obtained on the AAP web site: www.aap.org. Parents should also talk to their pediatrician.

------ The American Academy of Pediatrics is an organization of 55,000 primary care pediatricians, pediatric medical subspecialists, and pediatric surgical specialists dedicated to the health, safety and well-being of infants, children, adolescents and young adults.

------ Editor's Note: A b-roll package containing interviews with parents and pediatricians about the value of vaccines and images of children who have contracted infectious diseases, is available by calling Marjorie Tharp or Sherry Llewellyn at 202-347-8600.

Also: Information in this release is embargoed until 10:30 a.m. today (April 6).

-0- /U.S. Newswire 202-347-2770/

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Received by NewsEdge Insight: 04/06/2000 09:34:26

The Autism Autoimmunity Project

* ADDRESSING AUTISM * THROUGH IMMUNOLOGY

*definition * treatment * prevention*

(please scroll down)

Contents this page

Mission
Introduction and Vision Statement: *A Letter from the President*
Autism: An Immunological Perspective
Findings in Immunology: *Vijendra K. Singh, Ph.D. : Selected Research on Autism*
Contact information: Memberships / Donations / Publications

Contents, continued

MISSION

The Autism Autoimmunity Project is a non-profit charity dedicated to obtaining funding for

independent research addressing immune and immunogenetic abnormalities in autism.

The ultimate goals of Project research are to

1) fully define immune etiologies in autism;

2) develop appropriate treatment options for individuals who have autism through autoimmunity or immune system deficiency;
and to

3) develop mechanisms for prevention of immune-based autism, such as infant pre-vaccinal screening routines for immune and immunogenetic status.

* * * *

A Letter from the President

Lake Hiawatha, New Jersey
December 1999

Dear Friends,

The Autism Autoimmunity Project began, as you may know, with an idea I had early in 1998. The Project as a corporate entity was approved by the IRS in October 1998 as a 501 (c) (3) charity for autism research. At present, the Project has proposals out to several foundations, with the goal of multiplying our present total of $34,615 manyfold. This amount was recently disbursed to Dr. Vijendra K. Singh of Utah State University, Logan, and Dr. Andrew Wakefield of the Royal Free Hospital, London.

I started the Project after I had determined that other autism organizations weren't funding substantive immunological research. Also, that government support is lacking: for instance, when Dr. Bernard Rimland, Dr. V. K. Singh, Dr. Tina Zecca, Dr. Donatella

Graffino and I met with Marie Bristol-Power of the Centers for Disease Control, along with two associates from the National Institutes for Health on September 23, 1997, we were promised research support, but none came.

Our organization of parents and professionals must somehow enable crucial autism research to be done. Certainly, meaningful results will come only from the efforts of organizations like ours which are independent of both government and industry. Dr. Vijendra Singh was the inspiration for the Project, and I feel that his research of more than twenty years will be the key to obtaining definitive answers for our children with autoimmune indicators. I am sure that his work, and that of Dr. Andrew Wakefield, will in time make medical history.

Our organization has already supported several New Jersey-based autism initiatives: witness the recent passage of the $1.5 million New Jersey Autism Biomedical Research Act. This Act will channel funding toward immunological research in autism, within the state of New Jersey. Through my position on the Governor's Council I am working to secure significant funding for Dr. Oleske of the University of Medicine and Dentistry, New Jersey, via the Act. Still, these earmarked funds for autism education and research are unlikely to support the kind of research important to the Project: we must continue our efforts to fund research in immunology.

As the autism epidemic accelerates, a new vision has taken shape for an Autism Research Center wherein Drs. Singh and Wakefield, together with Drs. Harold Buttram and James Oleske, will combine their investigative efforts. For our proposed "center of excellence" to be created and sustained, however, it is estimated that a million dollars will be needed. As time goes on I envision that the research projects we fund will lead to new treatments for our children, as well as sound measures for the prevention of autism. We need solutions now--not forty to fifty years from now--and we need them to be derived from immunology- and environment-based study, rather than genetic research.

The answers we need are out there. With all of us working together, I am confident they will come to light soon.

Ray Gallup, President

Ray Gallup, President of the Autism Autoimmunity Project, is an accountant in private industry. Gallup's 15-year-old son, Eric, is featured in the book, "*Eric's Story: Autism and the Autoimmune Connection,*" available from the AAProject (see **Memberships/ Donations**...).

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DEFINITION

Autism: An Immunological Perspective by **Laura J. Ruede, M.L.S.**
Board Member, Autism Autoimmunity Project

Autism is an increasingly common developmental disability that typically appears in childhood, usually during the first three years of life, which curtails the normal development and functioning of the brain in the areas of reasoning, social interaction and communication. There may be emotional, motor and/or sensory disturbances which exacerbate these deficits. Frequently a developmental pattern is described depicting a period of normality, followed by either a sudden, or slow-but-steady, regression or loss of skills. Autism is typically defined by practitioners no further than a reference to its neurological basis, together with a list of its outward characteristics or symptoms. Coupled with this is an admission that the cause of the disability is unknown--for, tragically, the cause or causes of autism have been sought only in the area of genetics, from the time the condition was first described by Kanner in the 1940s.

Recent scientific findings have shown, however, multiple immune system abnormalities in autistic individuals. Scientists have also embraced the idea of the complex integration of the immune, nervous, endocrine, and other systems of the body; in particular the notion that early and severe derailments of the immune system can lead to profound neurological damage. Such derailments have been known to occur in conjunction with severe environmental insults, such as pre- or post-natal viral infections, or through vaccinations. The principal means by which such derailments can occur, however, is through genetic predisposition to immune system malfunction; such a predisposition has been described in autism by Warren, Singh, and others. The presence of viral or bacterial particles and/or antibodies in body tissues or fluids from persons with immune and/or neurological disease has been documented by A. J. Wakefield, in the case of autism, and repeatedly by many other scientists. A viral "insult" in predisposed persons can ultimately lead to a state of autoimmunity, or continuous immune reaction against the body's own tissues. Antibodies against brain and other body elements have been detected in autism by V. K. Singh.

The Causes of Autism and the Need for Immunological Research

References:

Cohen and Volkmar, Handbook of Autism and the Pervasive Developmental Disorders (New York: J. Wiley, 1997), chapter 18, "Medical Conditions: *Infections…Immunological Association*," page 398.

Isabelle Rapin, *Introduction and Overview* to Bauman and Kemper, The Neurobiology of Autism (Baltimore, Maryland: Johns Hopkins Press, 1994), pp. 13-14.

Uta Frith, Autism: Explaining the Enigma (Cambridge, Massachusetts: Basil Blackwell, 1989/1994), p. 79.

Trottier, et al., "*Etiology of Infantile Autism: A Review of Recent Advances in Genetic and Neurobiological Research*" (Journal of Psychiatry and Neuroscience, vol. 24, no. 2, March 1999, p. 103-115).

Van Gent, et al., "*Autism and the Immune System*" (Journal of Child Psychology and Psychiatry, vol. 38, no. 3, March 1997, pp. 337-349).

P. Szatmari, et al., "*Genetics of Autism: Overview and New Directions*" (Journal of Autism and Developmental Disorders, vol. 28, no. 5, 1998, pp. 355-365).

L. J. Ruede received her Master's degree in Library and Information Science in 1992 and is a member of Texas Christian University's professional staff, working with the Department of Communication Sciences and Disorders.

FINDINGS IN IMMUNOLOGY

Vijendra K. Singh, Ph.D. : Selected Research on Autism

Research Associate Professor, Utah State University, Dept. of Biology/Biotechnology Center
Scientific Board Member, Autism Autoimmunity Project

Dr. V. K. Singh received his doctorate from the University of British Columbia, Vancouver, Canada. His post-doctoral fellowship was completed in neurochemistry and neuroimmunology. Spanning over twenty years' experience in neurobiology and immunology research, Dr. Singh studied brain diseases, particularly infantile autism and Alzheimer's disease. Having authored over a hundred scientific publications, he is both a pioneer and an international authority on autoimmunity in autism. Dr. Singh is a member of the American Association for the Advancement of Sciences, the American Association of Immunologists, and the New York Academy of Sciences. He is listed in American Men and Women in Science (United States, R. R. Bowker, publisher) and The International Who's Who of Intellectuals (Cambridge, England, International Biographical Centre).

Introductions to the Work of V. K. Singh, Ph.D.

"*Autism, Autoimmunity and Immunotherapy: a Commentary,*" by Vijendra K. Singh, Ph.D., reprinted from the Autism Autoimmunity Project Newsletter, December 1999, http://lib.tcu.edu/www/staff/lruede/singhfeature.

"*Autoimmunity and Neurologic Disorders,*" an interview with V. K. Singh, Ph.D. in Latitudes (newsletter of the Association for Comprehensive NeuroTherapy, http://www.latitudes.org/index.html, vol. 4, no. 2, Spring 1999), by Sheila Rogers, is viewable at http://lib.tcu.edu/www/staff/lruede/latitudes.

"*Vijendra K. Singh, Ph.D.: Selected Work on Alzheimer's Disease*" lists immunological discoveries relating to Alzheimer's disease (http://lib.tcu.edu/www/staff/lruede/alzheimers).

V. K. Singh's "*Immunotherapy for Brain Diseases and Mental Illnesses*" (Progress in Drug Research), vol. 48, 1997, pp. 129-146) is a lengthy scientific article addressing the rationale for immunotherapy in brain diseases and possible applications of specific immunological therapies in Multiple sclerosis; Guillain-Barre syndrome; Rasmussen's encephalitis; Obsessive-compulsive disorder (OCD); Alzheimer's disease; and Autistic syndrome. The introduction to this article notes the growing comprehension among scientists of

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the reciprocal relationship between the nervous and immune systems, categorizes the various diseases of the nervous system, and observes that nearly all central nervous system diseases respond to immunotherapy.

Selected Research on Autism

"*Serological Association of Measles Virus and Human Herpesvirus-6 With Brain Autoantibodies in Autism.*" Clinical Immunology and Immunopathology, vol. 89, number 1, October 1998, pp. 105-8. This study is the first to report an association between virus serology and brain autoantibody in autism; it supports the hypothesis that a virus-induced autoimmune response may play a causal role in autism.

"*Positive Titers of Measles and Measles-Mumps-Rubella Antibody Are Related to Myelin Basic Protein Autoantibody in Autism.*" Abstract of study prepared for the annual meeting of the American Association of Immunologists (AAI) / Federation of American Societies for Experimental Biology (FASEB), San Francisco, April 1998. A significant number of autistic children exhibit positive titers of measles and MMR [measles-mumps-rubella] antibody, which in a vast majority of cases is associated with the presence of MBP [myelin basic protein, or brain] autoantibody. A measles- and/or MMR-triggered autoimmune response to myelin may play a pathogenesis role in autism.

"*Association of Anti-MBP and Anti-NAFP Antibodies With HHV-6 Antibodies in a Child With Autistic Regression.*" Journal of Allergy and Clinical Immunology, vol. 101, no. 1, part 2, S122, January 1998 (in section entitled, "Program and Abstracts of Papers to Be Presented During Scientific Sessions [at the] 54th Annual Meeting, March 13-18, 1998"). Children with autism have been shown to have a high incidence of circulating autoantibodies to myelin basic protein (MBP) and to neuron-axon filament protein (NAFP) compared with healthy controls or controls with other disabilities. Subacute viral infections of the central nervous system have been postulated to play a role in children who develop normally before undergoing autistic regression. In this instance, a healthy boy having a typical case of roseola (HHV-6) at 15 months experienced severe regressions of language and social behavior soon afterward. "The presence of antibodies against MBP and NAFP along with the clinical course and elevated levels of HHV-6 antibodies suggest an autoimmune response to this neurotropic virus[,] resulting in the autistic regression."

"*Circulating Autoantibodies to Neuronal and Glial Filament Proteins in Autism.*" Pediatric Neurology, vol. 17, number 1, July 1997, pp. 88-90. A significant increase in incidence of anti-NAFP [neuron-axon-filament-protein] and anti-GFAP was seen in autistic subjects, but not in mentally retarded subjects. Clinically, these autoantibodies may be related to autoimmune pathology in autism.

"*Hyperserotoninemia and Serotonin Receptor Antibodies in Children With Autism but Not Mental Retardation.*" Biological Psychiatry, vol. 41, number 6, March 15, 1997, pp. 753-5.

"*Elevated Serotonin Levels in Autism: Association With the Major Histocompatibility Complex.*" Neuropsychobiology, vol. 34, number 2, 1996, pp. 72-5. Two of the most consistently observed biological findings in autism are increased serotonin levels in the blood and immunological abnormalities (including autoreactivity with tissues of the central nervous system). The major histocompatibility complex (MHC) regulates the immune system, and is associated with autoimmune disorders. In this study, a positive relationship was observed between elevated serotonin levels and the MHC types previously associated with autism.

"*Plasma Increase of Interleukin-12 and Interferon-gamma. Pathological Significance in Autism.*" Journal of Neuroimmunology, vol. 66, numbers 1-2, May 1996, pp. 143-5. Immune factors such as autoimmunity have been implicated in the genesis of autism, a neurodevelopmental disorder. Since autoimmune response involves immune activation, the plasma levels of interferon-alpha (IFN-alpha), IFN-gamma, interleukin-12

(IL-12), and IL-6 were measured, along with tumor necrosis factor (TNF-alpha) and soluble intercellular adhesion molecule-1 (sICAM-1). The levels of IL-12 and IFN-gamma were significantly higher in autistic patients than in controls (the remaining measures were not significantly different). It is suggested that IL-12 and IFN-gamma increases may indicate antigenic stimulation of Th-1 cells pathogenetically linked to autoimmunity in autism.

"Immunogenetic Studies in Autism and Related Disorders." Molecular Chemistry and Neuropathology, vol. 28, numbers 1-3, May-August 1996, pp. 77-81. The major histocompatibiligy complex comprises a number of genes that control the function and regulation of the immune system. One of these, the C4B gene, encodes a product that is involved in eliminating pathogens such as viruses and bacteria from the body. A deficient form of the C4B gene, termed the C4B null allele (no C4B protein produced) was previously seen to have an increased frequency in autism. In this study, this finding was confirmed, and this same condition was detected in related [neurodevelopmental] disorders as well. In addition, two alleles of the DR beta 1 gene also had significantly increased representation in autistic subjects.

"Antibodies to Myelin Basic Protein in Children With Autistic Behavior." Brain, Behavior and Immunity, vol. 7, number 1, March 1993, pp. 97-103. Approximately 58% of the sera of autistic children were found to be positive for anti-MBP [anti-brain antibodies]. This result was significantly different from that of the controls, among whom were children with normal health, idiopathic mental retardation, and Down syndrome. It is possible that anti-MBP antibodies are associated with the development of autistic behavior.

"Possible Association of the Extended MHC Haplotype B44-SC30-DR4 With Autism." Immunogenetics, vol. 36, number 4, 1992, pp. 203-7. The complement C4B null allele appears to be associated with infantile autism. In this study, the incidence of B44-SC30-DR4 was increased by almost six-fold in the autistic subjects as compared with healthy controls. Moreover, the total number of extended haplotypes expressed on chromosomes of autistic subjects was significantly increased as compared with those expressed on chromosomes of healthy subjects. Conclusion: a gene related to, or included in, the extended major histocompatibility complex may be associated with autism.

"Increased Frequency of the Null Allele at the Complement C4b Locus in Autism." Clinical Experiments in Immunology, vol. 83, number 3, March 1991, pp. 438-40. Associations between C4 deficiency and autoimmune disorders have been found over the past several years. In this study, autistic subjects and their mothers had significantly increased phenotypic frequencies of the C4B null allele, compared with controls. The siblings of the autistic subjects also had an increased frequency of the C4B null allele, but this was not significant. The fathers did not display this allele. All family members had normal frequencies of the C4A null allele, all normal C4A and C4B alleles and all BF and C2 alleles.

"Changes of Soluble Interleukin-2, Interleukin-2 Receptor, T8 Antigen, and Interleukin-1 in the Serum of Autistic Children." Clinical Immunology and Immunopathology, vol. 61, number 3, December 1991, pp. 448-455. Findings indirectly indicated that the activation of a subpopulation of T cells occurs in some children with autism, as opposed to healthy children or children with mental retardation (non-Down's syndrome).

"Deficiency of Suppressor-inducer (CD4+CD45RA+) T Cells in Autism." Immunological Investigations, vol. 19, number 3, June 1990, pp. 245-51. Autistic subjects as compared to a group of 35 healthy age-matched subjects had a significantly reduced number of lymphocytes, a decreased number of CD2+ T cells and reduced numbers of CD4+ and CD4+CD45RA+ lymphocytes. Results suggest that an alteration in the suppressor-inducer T-cell subset is associated with autism.

"CD4+ Helper T Cell Depression in Autism." Immunology Letters, vol. 25, number 4, September 1990, pp. 341-5. Autistic subjects had a significantly lower percentage and number of CD4+ cells, a lower

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number of T cells (CD2+ cells) and B cells (CD20+ cells), and a lower percentage and number of total lymphocytes than siblings and normal subjects. The level of blood values for female subjects appeared lower than those for males as compared to normal subjects of the same sex. Results suggest that a decrease in CD4+ cells is associated with autism.

MEMBERSHIPS / DONATIONS / PUBLICATIONS

The Autism Autoimmunity Project is a non-profit charity dedicated to obtaining funding for independent research addressing immune and immunogenetic abnormalities in autism. The ultimate goals of Project research are to
1) fully define immune etiologies in autism; 2) develop appropriate treatment options for individuals who have autism through autoimmunity or immune system deficiency; and to 3) develop mechanisms for prevention of immune-based autism, such as infant pre-vaccinal screening routines for immune and immunogenetic status.

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___ I would like to become a member of AAP at $25.00 per year ($30.00 overseas). Membership includes subscription to the

Newsletter, published in June and December. My membership expiration date will appear on the mailing label.

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Mr. BURTON. I see this as a little bit different situation. The pharmaceutical companies who are producing jobs—and they do a great job for the country—but they have a financial interest in getting things approved.

The New England Journal of Medicine has recognized this in a recent publication, on the front page. They said that they had some people on their advisory committees who had made some comments and made some recommendations that had financial interest, and they had not scrutinized them properly, and they apologized for it and said it would not happen again.

So what I asked Dr. Boyle and what I am inferring here today is that there can be a bias if people are being paid or reimbursed by pharmaceutical companies when they start making a decision or a recommendation on an advisory panel.

Now, you said that if they represent Merck or Bristol Meyers or some other laboratory, they will probably excuse themselves from voting, and there may be a requirement for that. That does not alter the fact that they are sitting on that panel, and they are talking to everybody else on that panel, and they have influence on that panel, and they do have a tremendous impact on whether or not certain things are approved or disapproved. And I think that that is a conflict of interest. I do not see why we cannot have people on advisory panels who have no financial interest whatsoever with pharmaceutical companies when they are approving those, because we are talking about the health of the Nation. And that is something which ought to be investigated very thoroughly by this Congress.

We are talking today about autism, but there is something of as great stake here as the autism question and whether or not the MMR vaccine and other vaccines may be contributing to autism, and that is are we letting pharmaceutical companies have too great an influence on the decisionmaking process that affects very one of our lives?

Right now, we are talking about the anthrax vaccine. They are going to inoculate every one of our military personnel, and there are all kinds of questions about the anthrax vaccine, all kinds of them. We have had all kinds of side effects that we have talked about, and I have talked to people who have had them. And the former chairman of the Joint Chiefs of Staff is on the board of that company that makes the anthrax vaccine. They are manufacturing millions of doses of this vaccine, and every member of the service will have to get six shots of that. If the decisionmaking process involves people who have a financial interest in it, and that outweighs the potential side effects of any drug, then I think there is something amiss.

So I have great concerns about that, and I would just say to you that HHS and CDC and FDA and all of them ought to take a hard look at whether or not they have people on their advisory panels who have a potential conflict of interest by getting money or something else from a pharmaceutical company that they represent.

Now, I was not trying to impugn the integrity of Dr. Offit, but I did want to point out that he does get money from Merck and gets some benefits from Merck. So for anybody to say that he can be totally unbiased is questionable. Maybe he would be totally unbiased, but it is questionable.

So I think that this whole issue of whether or not the MMR vaccine is a problem—the measles vaccine has been found in the gut, it has been verified, and we still have this problem, and the question was whether or not it goes from the gut up to the brain and is a contributing factor to autism—but the companies that make the MMR vaccine have people on the advisory boards who are participating in the decisionmaking process.

So it makes me wonder whether we are going to really get to the bottom of it unless we go to outside entities—and that is not questioning anybody's integrity. It is just saying that if I am paying somebody money for some product or something, and there is something else that I am going to make money off of, and they are on a board that is going to participate in a decisionmaking process, to say that they do not at least think about me and think about where the money is coming from just boggles my mind, and I think it would most people.

With that, do I have any further questions? Let us see what else we have here.

[Pause.]

Mr. BURTON. OK. Dr. Boyle, for your information, at a public meeting in Brick Township in January 1997—and you should know this—with CDC and others present, several audience members asked about the vaccines and the possible autism link, and they asked that vaccines be checked. That is from Andy Napoli, the legislative director of Representative Chris Smith.

So, I again want to stress that we want to have an answer from CDC. If parents from that township were wondering about the possible connection between these vaccinations and autism, why didn't CDC check on it? Why not? You are checking on everything else, the other environmental concerns around there. Why not check on the vaccine?

And I submit that maybe, just maybe, it is because the pharmaceutical company that manufactures it had some influence on the people who were in that meeting, and they said, Hey, we do not want to get into that. And if that is the case, that is damned near criminal.

With that, I will be happy to yield back the balance of my time and let Mr. Waxman have his 5 minutes. Then we will go to the next panel.

Mr. WAXMAN. Thank you, Mr. Chairman.

I would like to have Dr. Spiker come forward, if he would.

Dr. SPITZER. Spitzer. S-p-i-t-z-e-r.

Mr. WAXMAN. Oh. I am sorry. Dr. Spitzer, where are you——

Dr. SPITZER. I am a professor of epidemiology with the Faculty of Medicine at McGill University in Montreal.

Mr. WAXMAN. When you came forward a moment ago, you appeared to be reading from a prepared statement. Did you have a statement written out that you read from?

Dr. SPITZER. Yes, I did. The circumstances are that I personally learned of this hearing, and of related activities very late in the game. I have been an honorary assistant to 2,100 families in the

United Kingdom who have great difficulty getting scientific help and cannot afford it. I have chosen on this issue——

Mr. WAXMAN. Excuse me. Did you prepare that statement yourself before the hearing?

Dr. SPITZER. Yes, I did.

Mr. WAXMAN. OK. And were you contacted or did you contact Chairman Burton's staff before your testimony?

Dr. SPITZER. I did so indirectly, to the best of my knowledge, through a person named Ms. Barbara Fisher.

Mr. WAXMAN. And could you identify Barbara Fisher? Is she here?

Dr. SPITZER. She is here in the audience.

Mr. WAXMAN. Is she a staffperson for the committee?

Dr. SPITZER. No. She is in the vaccination——

Mr. WAXMAN. When did you talk to her? Was it today or earlier than today?

Dr. SPITZER. I spoke to her yesterday and the day before yesterday by telephone and met her here——

Mr. WAXMAN. And you met her here?

Dr. SPITZER. I met her this morning.

Mr. WAXMAN. But you talked to her yesterday and the day before about coming here to testify?

Dr. SPITZER. Yes.

Mr. WAXMAN. Thank you very much.

Dr. Offit——

Dr. SPITZER. I am sorry. It was primarily for the press conference, but with the possibility of being able to testify as well.

Mr. WAXMAN. Yes—some extenuating circumstances for which the rules did not have to be observed.

Dr. Offit, the chairman says he is not impugning your reputation, but it sounds to me like your reputation has been impugned. You get money from Merck. They make the vaccine. You are on an advisory committee for the CDC about vaccines. That is an apparent conflict of interest. Again, why isn't it a conflict of interest?

Dr. OFFIT. Because as I sit on the Advisory Committee on Immunization Practices and make recommendations for children in this country, the only thing I consider is exactly how I would treat my own children. I mean, I take the job very seriously. So the recommendations that I make are based solely on a careful review of the data that are presented to us, period. I do not have any conflict with regard to that decisionmaking process. It is simple in that sense.

Mr. WAXMAN. Dr. Boyle and Dr. Schwartz, what would happen if you excluded people from your advisory committee who worked in the area of research on vaccines or in some other area for a pharmaceutical company?

Dr. SCHWARTZ. Those with the greatest expertise on vaccines and those who are best able to make recommendations that will protect the health of American children have frequently done research in vaccines. They are the ones who know the issues best and who can make the best recommendations. By including them on the advisory committee, but implementing appropriate controls to make sure there are no apparent conflicts of interest, the CDC feels that they get the best advice to make the best public health recommendations.

Mr. WAXMAN. How about people who are funded by the Autism Autoimmunity Project—have you ever heard of that group?

Dr. SCHWARTZ. The ACIP meetings are all open public meetings. They are all——

Mr. WAXMAN. What is "ACIP?"

Dr. SCHWARTZ. The Advisory Committee on Immunization Practices meetings are all open meetings and are announced in the Federal Register. If someone from that particular institute wanted to come and share information or present to the ACIP, they would certainly be welcome to do so.

Mr. WAXMAN. And would you feel they have a conflict of interest if they are funded by an organization that wants to have scientists establish a certain conclusion?

Dr. SCHWARTZ. I think the most important thing that we need to consider is the quality of the scientific data and whether those data have been peer-reviewed, whether they have been considered by other scientists, and whether they have been replicated in other laboratories.

Mr. WAXMAN. So you think the most important thing is that Dr. Wakefield and Dr. Singh ought to disclose if they are funded by this group, and Dr. Offit ought to disclose if he is funded by Merck.

Dr. SCHWARTZ. I think disclosure is important, yes.

Mr. WAXMAN. And then you evaluate their science?

Dr. SCHWARTZ. Yes.

Mr. WAXMAN. Because ultimately what is at stake are the scientific questions that we want answered.

Dr. SCHWARTZ. That is exactly correct, and preserving the health of American children.

Mr. WAXMAN. Well, that, it seems to me, should be the goal of all of us, and I hope that hearings like this are to try to get to that result and not simply to further a particular point of view which could well be wrong, and if it is wrong, as I fear it may be, by advertising this particular point of view and scaring the public, we could see a drop in immunization rates. And we do not know if autism will drop—in fact, we have evidence from Great Britain that it did not drop when immunizations did——

Mr. BURTON. I am allowing you extra time because I have one more question. I am allowing you extra time.

Mr. WAXMAN [continuing]. I am getting extra time—for good behavior—that when we do have an example in the real world of sensational press about the link between autism and vaccinations, vaccination rates dropped, and we knew that caused an increase in measles, but we saw no decrease in autism.

It is troubling to me. I appreciate all of the views that have been expressed here, and I hope that we can get an independent group to look at this, because I do not think this committee is an independent group trying to reach an honest conclusion.

I yield back the balance of my time to the chairman.

Mr. BURTON. Let me just make one final comment, and that is that the people who are doing the independent studies here do not sit on any advisory boards that are making decisions on what kinds of vaccinations we are going to be giving to the people of the

United States of America. The people who represent the pharmaceutical companies and sit on those boards do. That is the difference.

And let me just conclude by saying that I really appreciate all of you being here. This is a very difficult issue. I think it was unavoidable that there would be this kind of contention today because we have a lot of parents and grandparents, like myself, who feel very strongly about the life that our kids and grandkids are going to have to lead; and on the other side of the issue are the people who are saying there is no impact from the shots that are being given to our kids.

So the bottom line is that there are going to be strong differences of opinion, and we want to get all those differences of opinion on the record, and then we will all go out and have a cup of coffee together and debate it in private.

The American people need to know the facts. Lincoln said, "Let the people know the facts, and the country will be saved," and I think that is just as true today as it was at the beginning of this Republic. So that has been our goal—not to fight with everybody, but to get the facts out. And we are all for vaccinations. It is just do we want to give a child nine vaccinations in 1 day; do we want to give them 31 or 32 or 33 vaccinations between the time they are born and age 6? Isn't that maybe a little bit of overload? That is the whole question.

I want to thank this panel. We have one more panel. I really appreciate all of you being here, even though we may have some differences with some of you.

Thank you.

I apologize to the next panel for having to sit there for so long.

While the next panel is coming up, we will take a couple-minute break. The next panel consists of Dr. Bernard Rimland, Dr. Michael Goldberg, Dr. Mary Megson, Dr. John Upledger, Dr. Catherine Pratt, Dr. Deborah Hirtz, and Dr. Edward Cook.

We will start in just 1 minute.

[Recess.]

Mr. BURTON. The committee will reconvene.

Would everybody please take their seats and shut the doors, please?

I appreciate very much your patience today. Would the panel please rise?

[Witnesses sworn.]

Mr. BURTON. Have a seat, please.

We will start with you, Dr. Rimland.

STATEMENTS OF BERNARD RIMLAND, Ph.D., AUTISM RESEARCH INSTITUTE, SAN DIEGO, CA; DR. MICHAEL J. GOLDBERG, DIRECTOR, NIDS MEDICAL ADVISORY BOARD, TARZANA, CA; DR. MARY N. MEGSON, PEDIATRIC AND ADOLESCENT ABILITIES CENTER, RICHMOND, VA; DR. JOHN E. UPLEDGER, THE UPLEDGER INSTITUTE, CLEARWATER, FL; CATHY L. PRATT, INDIANA RESOURCE CENTER FOR AUTISM; DR. DEBORAH G. HIRTZ, NATIONAL INSTITUTES OF HEALTH; DR. EDWIN H. COOK, JR., UNIVERSITY OF CHICAGO

Mr. RIMLAND. Thank you very much for the opportunity to be here. It is a great honor and a great privilege.

I want to start by commenting that there has been a lot of discussion during the past few hours about the supposedly unproven hypothesis that vaccines may cause autism. There is another unproven hypothesis which has been unchallenged and unquestioned, at least relatively so, and it is really a very important hypothesis, and that hypothesis is that vaccines are safe.

The real hypothesis which should have been tested years and years and years ago by much more scientific research than has ever been devoted to it is the proposition that vaccines do not cause damage. The Vaccine Information Adverse Reaction Reporting System has not been studied; it has not been looked at at all carefully, and therefore, the assumption that many people are making is that the vaccines have been looked at carefully for adverse reactions, and they have not been.

The other point I want to make has to do with the testimony of Dr. Brent Taylor, who spoke here on the last panel. I was very bothered by the lack of information and the confusing information in his paper. My entire life has been spent as a professional researcher—almost 50 years of my life has been as a full-time professional researcher. I am a fellow of the division of statistics, measurement and evaluation of the American Psychological Association.

I wrote a friendly letter to Dr. Taylor indicating that I would very much like to take a look at his data, because I did not understand part of it, and there were some questions that I wanted to raise. He ignored my first letter. I sent a second letter, and he responded to that by saying no, I could not have a look at his data.

I then wrote to the editor of the Lancet urging that a blue-ribbon committee be appointed to take a very close look at the data of Dr. Taylor. So I am delighted that you have asked for it as well.

My own son Mark was born in 1956 as a severely autistic child from birth. Our pediatrician, who had been in practice for 35 years at that time, had never seen such a child or heard of such a child.

When Mark was 2, my wife and I found the word "autism" for the first time in a textbook. I was at that point 5 years beyond my Ph.D. in psychology, never having heard of or seen the word "autism" before. It obviously was a very rare disorder, extremely rare. None of us had heard of it.

Today it is extremely common. There is hardly a high school kid in the country who has not heard of autism. It is a household word now, and that is not because of the movie "Rain Man," but because it is extremely prevalent.

Despite denials from some experts, there is a terrible worldwide epidemic of autism. In the mid-1960's, after my book "Infantile Autism" was published, I began hearing from parents throughout the world whose children had been normal until given the DPT shot. I began to make note of it and ask questions about it in the form letters I sent out to parents seeking information about autism.

In the past few years, the Autism Research Institute, which I direct in San Diego, has been flooded with letters and faxes about children whose parents say and can prove very well with videotapes and photos that their kids were normal until getting another triple vaccine, the MMR shot. In my view, the evidence is overwhelming that vaccines, especially the triple vaccines, and among the triple vaccines especially the MMR, can and do cause many cases of autism.

It is also alarming but true that 90 to 99 percent of adverse reactions to vaccines are never reported. There is no penalty for a doctor's failure to report a bad vaccine reaction, so they simply do not do it. Why should they engage themselves in paperwork if there is no requirement that they do it and no penalty for not doing it?

This being so, how can the authorities claim that the vaccines are safe, given that only 1 to 10 percent of adverse events are ever reported? Doctors must be trained to recognize, and required, not just requested, to report adverse events.

With regard to the question of genetics, they say that autism has a large genetic component, and therefore, vaccines must play a minimal role. My book, "Infantile Autism," published in 1964 was the first systematic attempt to marshal the evidence for a genetic relationship to autism, so I am certainly not hostile to that idea. However, genes do not begin to account for the huge increase in the incidence of autism. There is no such thing as an epidemic due to gene problems. The increase ranges from 250 to 500 percent in various places, as other people have pointed out here.

As the editor of the Autism Research Review International, I have just reviewed a very large number of studies on the genetics of autism. The next issue of the Autism Research Review is going to contain our review study. The results of our review are spectacularly inconsistent. The best guess is that there are at least 20 different genes that may be involved in the causation of autism. Genes are not the answer to the question, even though, at one time, I was very much in favor of looking at that hypothesis. I am still interested in the hypothesis, but it is certainly not responsible for the increase in autism.

The people who claim that the vaccines are safe claim that autism naturally occurs at about 18 months, when the measles/mumps/rubella vaccine is routinely given, so the association is merely coincidental and not causal. But the onset of autism at 18 months is a recent development. Autism starting at 18 months rose very sharply in the mid-1980's, when the MMR vaccine was introduced. For the previous 30 years—we have been collecting information from children born in the fifties, sixties, seventies, and so forth—there were twice as many kids reported with the autism started at birth as there were kids whose parents reported that the autism started at 18 months.

Starting in about the 1980's, when the MMR vaccine was introduced, those two curves converged. Over a period of several years, the number of kids whose autism started at 18 months rose to twice as high as the number starting at birth. On the last page of my handout, I have a graph that shows those curves based on the records of over 31,000 children in our San Diego institute. So that particular argument against the MMR hypothesis is obviously a very poor one.

Autism is not the only severe chronic illness which has reached epidemic proportions, as the number of very profitable vaccines has rapidly increased. Children now receive 33 vaccines before they enter school—a huge increase. The vaccines contain not only live viruses, but also very significant amounts of highly toxic substances such as mercury, aluminum and formaldehyde. Could this be the reason for the upsurge in ADHD, asthma, arthritis, Crohn's disease, lupus, and other chronic disorders? It seems as though we are trading protection against acute diseases such as measles and mumps for a huge epidemic of chronic diseases like autism, asthma, and the others I mentioned.

As a parent and a full-time professional researcher, I am bitterly disappointed with the medical establishment's dismal record with regard to autism over the past 60 years. The medical schools as well as the Government agencies have consistently supported outmoded, unproven and even disproven ideas, including the one that autism was caused by "refrigerator mothers" who did not love their children, thus causing autism. The medical establishment was opposed to behavior modification, or what is now called the ABA approach. They said that this was not a way to treat autism, because autism was based on deepseated emotional problems, so a technique that is used to train animals cannot be used to improve autistic children. That was untrue. They have ignored and continue to ignore the long series of studies conducted both in the United States and Europe showing that the elimination of foods containing gluten and casein from the diet brings about marked improvement in many autistic children. They have consistently ignored the series of 18 consecutive studies conducted by researchers in six countries which show that almost half of all autistic children and adults respond favorably to high doses of Vitamin B6 and magnesium, with no adverse reports from any of these studies. Eleven of these studies were double-blind placebo-crossover experiments. There is no drug which comes even close to B6/magnesium in terms of safety, efficacy, and positive research findings, yet it is not being explored at all.

Tens of millions of dollars have been spent on nonproductive lines of research while virtually no money at all has been given to research on methods of alternative medicine which are far more promising in terms of both safety and efficacy.

The most interesting questions are not being asked. Why does the majority of any population survive such epidemics as autism, the bubonic plague, Legionnaire's disease, polio and AIDS, while relatively few succumb?

The very obvious answer and the most probable answer is that the survivors have healthy, effective immune systems. Would enhancing the immune system decrease the likelihood of adverse reactions to vaccines—including, by the way, the anthrax vaccine. I hope that DOD will pay some attention to that. There is good reason to think about anthrax in this context.

It is well-known that the immune system must be adequately supplied with many nutrients if it is to function properly, including especially Vitamins A, C, E, B6, and a number of minerals, including zinc, magnesium, and selenium. Nutritional levels of these substances are not only harmless, but they are essential to good health.

Since people do not change their diets readily, I believe that foods should be fortified with these nutrients, especially foods which will be consumed by infants and children. Research along these lines, as well as on the safety of the vaccines, is desperately needed.

Recently, Professor Clementson published a paper—he is the author of a three-volume treatise on Vitamin C—reviewing the evidence showing that individuals who are vaccinated without having adequate supplies of Vitamin C in their bodies are far more likely to suffer an adverse reaction to the vaccine than those who have higher levels of Vitamin C.

Dr. Archie Kalokerinos of Australia, a pediatrician assigned by the Government to the outback people there, found an infant death rate of 50 percent among the children he cared for. They died soon after the vaccines. He found that they were extremely Vitamin C-deficient, and he learned that by giving them some extra Vitamin C, he could prevent their deaths. The death rate went from 50 percent to zero in a very short time. Dr. Kalokerinos was given a medal by the Australian Government.

We should be giving our children Vitamin C as well as other nutrients to make sure that their immune systems are well-fed and function well. I think we would see a lot fewer of the problems that we are experiencing today.

As a parent and as a researcher, I believe there should be a marked redirection of effort and funding along the lines suggested above.

Thank you.

Mr. Burton. Thank you, Dr. Rimland. I appreciate your comments.

Dr. Goldberg.

[The prepared statement of Dr. Rimland follows:]

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Testimony of Bernard Rimland, Ph.D.
before House Committee on Government Reform
April 6 2000

The Autism Increase: Research Needed on the Vaccine Connection

My name is Bernard Rimland. I am a research psychologist (Ph.D.), and am Director of the Autism Research Institute, which I founded in 1967. I am also the founder of the Autism Society of America (1965), and the editor of the Autism Research Review International. My book, Infantile Autism: The Syndrome and Its Implications for a Neural Theory of Behavior (1964) is widely credited with changing the field of psychiatry from its claim that autism is an emotional illness, caused by destructive mothers, to its current recognition that autism is a biological disorder. I have lectured on autism and related problems throughout the world, and am the author of numerous publications. I served as primary technical advisor on autism for the film **Rain Man**.

My son Mark was born in 1956. It was obvious from birth that this perfectly normal-looking infant had something drastically wrong with him. I had earned my Ph.D. in experimental psychology 3 years earlier and had never encountered the word autism. Our pediatrician, with 35 years of experience, had never heard of autism either. Autism was extremely rare then -- it is extremely common now.

Some supposed experts will tell you that the increase reflects only greater awareness. That is nonsense. Any pediatrician, teacher or school official with 20 or more years experience will confirm what the studies tell us: There is a real increase in autism and the numbers are huge and growing. The epidemic is serious and world-wide.

Soon after my textbook on autism was published in 1964, I began to hear from other parents. Many parents told me that their children were normal until getting a triple vaccine -- the DPT shot. In 1965 I began systematically collecting data on the symptoms and possible causes of autism: In 1967 I began querying the parents -- 33 years ago -- specifically about the child's response to the DPT shot. Many had reported marked deterioration.

During the past few years the Autism Research Institute has been flooded with an upsurge in pleas for help from parents throughout the world -- from wherever the World Health Organisation vaccine guidelines are followed. The majority of these parents say their children were normal until getting the MMR -- another triple vaccine.

Let me dispel several myths promoted by those who deny the autism-vaccine connection:

1. They claim the vaccines are safe, but physicians are indoctrinated to disbelieve claims of harm and are not trained to recognize nor required to report any adverse reactions. From 90% to 99% of the adverse reactions reported to doctors

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are never reported by those doctors to the government's extremely lax Vaccine Adverse Event Reporting System, known as the VAERS.

2. They say that the suspected linkage between the MMR vaccination and autism has been disproved by a study conducted by Brent Taylor and his colleagues in London, and published last year in The Lancet. The Taylor study is seriously flawed in many ways, as has been noted in a number of letters to the editor of The Lancet and in a number of additional letters on the subject which have been posted on the internet. It was subject to strong attack at a recent meeting of the British Statistical Society. I have been a full-time researcher my entire professional life, for almost 50 years, and I respectfully asked Dr. Taylor for a copy of the data so that I could reanalyze them. He refused this ordinary professional courtesy, and I have subsequently written to the editor of The Lancet requesting that an impartial committee be asked to reexamine Dr. Taylor's statistical methods. If he refuses again, I urged the The Lancet to retract his paper.

3. They say that autism has a large genetic component, and therefore vaccines must play a minimal, if any, role in the causation of autism. My book Infantile Autism, published in 1964, was the first systematic attempt to marshall the evidence for genetics as a contributing cause of autism, so I am certainly not hostile to that idea. However, genes do not begin to account for the huge increase in the incidence of autism, ranging from 250% to 500% in various places. I might add that we have just reviewed all of the recent genetic studies for the next issue of the Autism Research Review International, which I edit. The results are spectacularly inconsistent. The best guess is that there are at least 20 different genes involved in the causation of autism. Gene therapy is decades off, and may be infeasible.

4. They claim that autism naturally occurs at about 18 months, when the MMR is routinely given, so the association is merely coincidental and not causal. But the onset of autism at 18 months is a recent development. Autism starting at 18 months rose very sharply in the mid-1980s, when the MMR vaccine came into wide use. A coincidence? Hardly! See the graph below.

Autism is not the only severe chronic illness which has reached epidemic proportions as the number of (profitable) vaccines has rapidly increased. Children now receive 33 vaccines before they enter school -- a huge increase. The vaccines contain not only live viruses but also very significant amounts of highly toxic substances such as mercury, aluminum and formaldehyde. Could this be the reason for the upsurge in autism, ADHD, asthma, arthritis, Crohn's disease, lupus and other chronic disorders?

As a parent and as a full-time professional researcher, I am bitterly disappointed with the medical establishment's dismal record with regard to autism over the past 60 years. The medical schools, as well as the governmental agencies, have consistently supported outmoded, unproven and even disproven theories from the very beginning, and have actively opposed the most promising approaches for the treatment of autism. They supported the psychoanalytically-based theories which

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held the mother responsible for causing autism through her supposedly hostile attitude toward the child. They opposed the use of behavior modification, the most uniformly beneficial treatment for autism, by claiming that it neglected the deep-seated emotional blocks that were supposedly at the root of autism. They have ignored, and continue to ignore, the long series of studies conducted both in the U.S. and Europe showing that the elimination of foods containing gluten and casein from the diet brings about marked improvement in many autistic children. They have consistently ignored the series of 18 consecutive studies, conducted by researchers in 6 countries, which showed that almost half of all autistic children and adults respond favorably to high doses of vitamin B6 and magnesium, with no adverse effects. Eleven of these studies were double-blind placebo-crossover experiments. There is no drug that comes close to B6/magnesium in terms of safety, efficacy and positive research findings.

Tens of millions of dollars have been spent on non-productive lines of research, while virtually no money at all has been given to research on the methods of alternative medicine, which are far more promising in terms of both safety and efficacy.

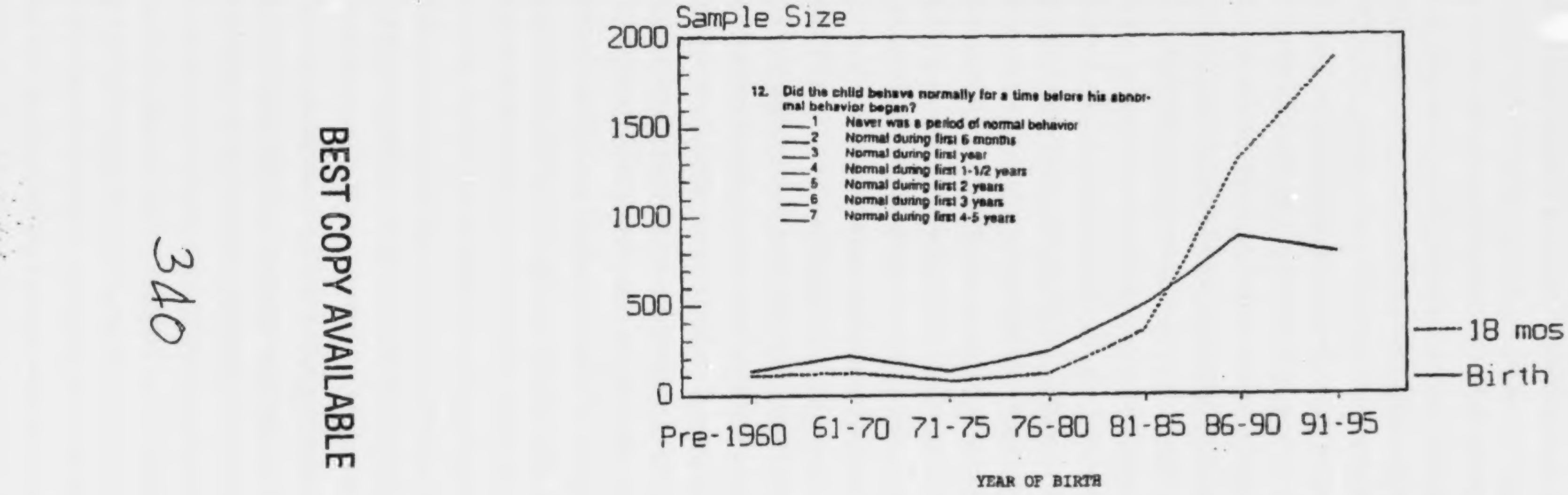
The most interesting questions are not being asked: Why does the majority of the population survive such epidemics as autism, the bubonic plague, Legionnaires' disease, polio and AIDS, while relatively few succumb?

The answer is that the survivors have a healthy, effective immune system. Would enhancing the immune system decrease the likelihood of adverse reactions to vaccines (including the anthrax vaccine -- DOD please note!)? Very probably.

It is well known that the immune system must be adequately supplied with many nutrients if it is to function properly, including especially vitamins A, C, E, B6 and a number of minerals, including zinc, magnesium, and selenium. Nutritional levels of these substances are not only harmless, they are essential to good health. Since people do not change their diets readily, I believe that foods should be fortified with these nutrients -- especially foods that will be consumed by infants and children. Research along these lines -- as well as on the safety of the vaccines -- is desperately needed.

As a parent and a researcher, I believe there should be a marked redirection of effort and funding, along the lines suggested above.

U.S. Cases
E-2: Year Born and Question 12
Behaved normally before abnormal ...?
Never Normal Period Vs. 18 mos



The officials of the American Academy of Pediatrics, Centers for Disease Control, and other medical organizations claim that since autism typically starts at about 18 months, when the MMR shot is"coincidentally"given, the parents are mistaken in their belief that the MMR caused their child's autism. To examine this issue, Rimland analyzed the data collected by the Autism Research Institute from many thousands of parents of autistic children since the 1960s.

The data reveal that the onset of autism at 18 months is a recent development. Parent reports show that through the 1960s, '70s and early '80s children autistic from birth outnumbered by 2 to 1 those with onset at 18 months. Starting in the early-1980s, when the MMR triple vaccine was introduced, the picture has reversed: now the "onset at 18 months" children outnumber the "onset at birth" children by 2 to 1.

Dr. GOLDBERG. Mr. Chairman and members of this committee, thank you for allowing me the opportunity to speak here today. I wish to take a moment to examine the urgency of this epidemic.

I am Dr. Michael Goldberg, a practicing pediatrician for over 20 years in Los Angeles, and I am on the clinical teaching staff of UCLA. I am also the founding member of the NIDS Research Institute, a parent-physician partnership developed to expedite research on behalf of children with special needs.

Out of necessity and a desire to help, my practice is comprised primarily of children with autism, ADD, and other special needs. I am here before you today to share my frontline, everyday experience with these children, experience that has overwhelmingly convinced me and my colleagues that this is a disease that can be treated.

In turn, I hope to propose a unique medical research model that combines the tenets of basic science and strong academics with an unprecedented sense of clinical urgency.

To understand this new autism that everyone keeps speaking about, one must actually step back and look at the increased understanding and incidence of autoimmune diseases across the board from the mid-1970's to the present date. All that one has to do is look at the medical literature to realize that every disorder we have associated as an immune-connected, immune-mediated defect of the immune system—lymphomas, multiple sclerosis, Alzheimer's, lupus, ulcerative colitis, irritable bowel syndrome, rheumatoid disease, and even aging—have all become recognized as in part an autoimmune process or illness. As Dr. Galpin, an authority in infectious disease immunology and a pioneer in the application of immune-modulators and a member of the NIDS Medical Board likes to say: The friendly fire of our own bodies causes the damage.

We either have to assume that the increase in these disorders in the human population is mass hysteria, mass psychosis, schizophrenia and/or behavioral-developmental disorders, as was thought in the old days, or we need to step back and realize that maybe we have a large number of adults and children suffering a disease process that is affecting how their brain and nervous system functions. I have family after family within my new practice in which there is a mother or a father with chronic fatigue syndrome, an older child with ADD/ADHD, and a young child or two with autism/PDD.

Unless we assume that this is all random, unfortunately, there is a logical connection between the above disorders and the rapid emergence of this crisis. We must rapidly realize that almost all of these disorders result from a treatable disease process.

When you look at the factors among the children that I am seeing, many of them have low natural killer cells. These are part of the findings being reported in many of those other disorders. Another frequent finding is the presence of active HHV–6 virus and other related herpes viruses in some of these children. Similar findings are being reported for various adult autoimmune disorders, and recently, even the Centers for Disease Control published an article focusing on our emerging knowledge of HHV–6 and related disorders.

Fortunately, while people talk about the unknown entity of autism, I can show you picture after picture after picture that has allowed me with the help of researchers, Dr. Ismael Mena and Dr. Bruce Miller, to look at NeuroSPECT scans and understand what is going on in the brains of these children. For the majority, there is a decrease of blood flow and function of the temporal lobe of the brain, areas that are consistent with that predicted by neuro-anatomists.

We have a large collection of scans that show a decrease in blood flow that is reproducible, quantifiable. Blood flow corresponds directly to function. When compared to MRIs and CAT-scans, they help to confirm no pre-existing damage but rather point toward a neuro-immune direction etiology. In fact, as we learn more through imaging and scans and technology about the brain, in a recent New England Journal of Medicine article a year ago, they discussed the immune-brain-endocrine connection in the hippocampus, a system that, with the CA1 and CA2 nuclei and neuron, affects cognitive function, fatigue, and memory.

Today I have come to look upon this as a reversible condition. Thankfully, many children return to normal/above normal functioning by combining steps reflecting diet control, a combination of antivirals, antifungal, and low-dose SSRIs.

Parents who are told that their children will never be independent, will never be able to earn a living, will 1 day might have to be placed in an institution, have seen their children become top of their class academically. I have children within the practice scoring in the 97th and even the 99th percentile in California and Illinois State testing. This past week, a mother came to me with her 5-year-old child, who has been with me in the practice for about 8 months. She related an instance where the child said, "Mom, do you want me to pretend I cannot talk? Remember when I could not talk?"

We have so misunderstood and misjudged these children. What harm are we doing to these children as a result?

Hopefully, tomorrow, we will see new agents which will let us work better with the immune system. If we can focus a unified effort to identify a subspecialized set of immune markers, that will let us understand which patient is the most likely candidate for which immune agent, separate out this mixed group of children into logical subgroups.

In my written submission to the committee, the NIDS Medical Board outlines a hypothesis which is supported by over 60 journal references on children with autism and the neuro-immune disease process that is potentially reversible.

It is interesting to note that that hypothesis has been reviewed by at least four pharmaceutical companies, and there are no holes or deficits in that hypothesis.

Within the NIDS Institute, our researchers are all heavily credentialed, and many are involved in current NIH projects and other activities at the NIH and the FDA. Using this technology, their past experience, and a computerized data base, we can unify researchers in institutions across the country. We can literally pick and choose top physicians and researchers around this country and around the world to focus on the crisis it has become.

For instance, I am pleased to announce that members of the Mind Institute are hopefully looking at joining and combining efforts, and my hope would be that many independent groups can focus in a scientific manner on answering the questions being raised by this committee today.

Another significant benefit of exploring this disease process with a sense of urgency would be the unprecedented ability to screen children who might be susceptible to vaccines or any other factors which have been implicated as potential roles in subsets of these children. Any injury or loss of a child that could have been prevented remains unacceptable. There is no way to adequately console the parent of a lost or damaged child.

If focused correctly, we do have the ability to accelerate understanding and identification of potentially high-risk children. If we can identify these children, adjust their vaccine schedule appropriately, we have begun the process of stemming this epidemic and will have created a preventive health policy which would be part of a collective legacy for generations to come.

In 1996, I was a speaker at the Autism Society of America, attended by over 2,000 parents and professionals. My wife made the comment: "Where are the M.D.s?" The medical community had essentially abandoned these children once they became labelled as autistic.

The NIDS Medical Board is designed to help logically, academically, scientifically circumvent the expected learning curve as we see physicians coming back into this field make a radical shift in direction and orientation from what we might have been taught as physicians.

I plead with you, Mr. Chairman and members of the committee. These children are supposed to be a productive part of this country's future, not a health cost and burden. These children have the potential for full, productive, intelligent lives. Contrary to the old idea, their genetics are not the determining factor. A child cannot develop normally, develop some language, and lose it all, except in a disease process. We can apply good, sound science and logic to help solve the crisis now.

We must embrace what is literally a paradigm shift in the world of medicine and begin to view autism and other related classifications like we do Alzheimer's disease, cystic fibrosis, childhood cancer, and multiples sclerosis. Tragically, if we accept the status quo, we will be sacrificing millions of kids and will likely lose more in subsequent generations.

I implore you to investigate the concepts I have introduced, evaluate them, test them—do whatever it takes to convince you that we have a crisis for which inaction is politically and medically more risky than action.

I am extremely fortunate to have three healthy children and one healthy grandchild. I selfishly want the rest of my future grandchildren, all of yours, and others out there to have the same chance.

Thank you.

Mr. **BURTON**. Thank you, Dr. Goldberg. As I think you can probably guess, we are going to pursue this for a long time.

Dr. **GOLDBERG**. I hope so.

[The prepared statement of Dr. Goldberg follows:]

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April 6, 2000

Gentlemen,

I am Dr. Michael Goldberg, a Fellow of the American Academy of Pediatrics and Director of the non-profit NIDS Medical Board and Research Institute. I wish to thank all of you for giving me the opportunity to speak here today and for taking the time to examine the urgency of this epidemic.

I have put together a packet of articles detailing my scientific hypothesis and current treatment philosophy. I suggest they be included in the record. I have also provided information on the emerging science and technology describing Neuro Immune Dysfunction whose common pathway is involved in many immune or autoimmune diseaseas including the development of the Autistic Syndrome. We finally have an understanding of how the brain interrelates with the endocrine and immune system. We are confident that we can apply this new understanding rapidly to evolve a treatment plan within the next six to twelve months, through an unprecedented blend of private enterprise and government-supported research.

The purpose of this hearing is to investigate why we have a large increase in this phenomenon that we have called autism. But to understand that, one must step back and look at the increased understanding and incidence of auto-immune disorders across-the-board, from the early/mid 1970's, when I completed my medical training, to the present day. All one has to do is look at the medical literature to realize that nearly every disorder we have associated as immune connected, immune-mediated, defects in the immune system - lymphoma, multiple sclerosis, Alzheimer's, lupus, Ulcerative colitis, rheumatoid disease, and even aging - have all become recognized as in part autoimmune diseases or illnesses where the friendly fire of our own bodies causes the damage as my colleague Dr. Galpin, an infectious disease and immunology authority, often is quoted to say.

If we are going to save this generation of children from a lifetime of suffering the incurable stigma of being diagnosed with autism and other cognitive delays, we must rapidly realize that all of these disorders result from a treatable rather than untreatable disease process. As written in the enclosed articles, and as a pure basic fact of science, it is medically impossible to have an epidemic of a genetic or developmental disorder. Further, while many have spoken of an "epidemic of autism," the truth is: the disease process many of these children have is not autism (as taught to physicians 30 – 40 years ago).

If a child is born developmentally miswired, "damaged", something happened in utero. But, a child cannot learn to speak and use language and then lose these abilities if the cause of their disorder is developmental, structural, etc. Such a child cannot respond to treatment and become a regular child once more, as has been the case in my practice over and over again, if the cause of their disorder is a "fixed" process, congenital or genetic disorder. It has been repeatedly apparent that 4, 5, 6 yr. old children are starting over where they left off at 18 months, 2 years of age. Parents who were told their children would never talk, could never be social, could never have feelings, now have children who are normal functioning or who are still struggling to catch up and get back to that fully normal functioning child, in either case these parents can see or are beginning to see a future for their child. It is my intent and hope in the time I have here, and through the articles I have submitted, to sow the realization that we are not talking about saving the next generation of children, but rather that we must focus our efforts on saving this generation of children before it is too late. The ramifications are enormous.

At the end of a research symposium in October 1997, one which brought together top researchers from around the country to discuss Alzheimer's, adult dementias, social brain, and Autism/Pervasive Developmental Disorder (PDD), this statement was made: if a child developed normally during the first twelve, fifteen, eighteen months of life, developed any language/words, and then somehow went into the autistic spectrum, it was a 100 percent certainty that the process had to be immune/viral. IF a child developed normally the first 12, 15, 18 months of life and had NO words, 99% it was an immune / viral process, and no one there could rationalize any other possible mechanism.

While there is ongoing controversy regarding past brain biopsy findings and their implications, if any, to this generation of children, we do have NeuroSPECT Scans, which show reproducible, quantifiable blood flow in the brain. Blood flow corresponds directly to function. When NeuroSPECT Scans of children diagnosed as autistic/PDD have been correlated with MRI's and CAT Scans, the combination consistently shows no pre-existing damage to the brain, but rather points toward an immune shutdown consistent with that found in adults with Chronic Fatigue Syndromes and other adult dementias and with children diagnosed as quiet ADD and mixed ADD.

I stumbled into the field of autism somewhat by accident. My wife had had Chronic Fatigue Syndrome for over ten years. Jokingly, my son asked me "Why are you sending Mom all over the country to doctors? Why don't you just fix her?" That began my journey into clinical research. It rapidly became apparent we were dealing with some component of the immune system, an autoimmune like reaction. During that time, as I was investigating all options for my wife, a few "Autistic" children were referred to my practice. Much to my surprise, these children had blood work comparable to that of my wife and other adults with this undiagnosed disorder, and to that of children I had been seeing diagnosed with quiet ADD and mixed ADD. I remember thinking then, "What could the immune system have to do with autism?"

Paralleling this, beginning in the 1980's was the initially slow, now epidemic incidence of disorders in children labeled as Autism/PDD and the increase of reports of autoimmune diseases in the animal literature, of altered ecological balance, immune system abnormalities in various species. We either have to assume that this increase of disorders in the human population is mass-hysteria, mass-psychosis, schizophrenia, and/or behavioral developmental disorders in children or we must step back and realize that maybe we have a large number of adults and children suffering from a disease process that is affecting how their brain and nervous system functions, in ways that physicians had never understood (or had the technology to understand). I have family after family within my "new" practice in which there is a mother or father with Chronic Fatigue Syndrome, an older child with ADD/ADHD, and a younger child or two with Autism/PDD. As noted, unless we assume this is all random, there is unfortunately a logical connection between the above disorders and their rapid emergence as a crisis.

We are looking at what appears, supported by increasing data and reports in the literature, to be auto-immune, Neuro-immune disorders or what my associates and I have termed Neuro Immune Dysfunction Syndromes or NIDS. If you are an adult with an intelligent, developed brain or an older teenager, when this process attacks, you will likely end up being diagnosed with the illnesses known as Chronic Fatigue Syndrome, Adult ADHD, etc. If you are a younger child, five, six, seven, or eight years old when this process is triggered, with some cognitive, social and language capabilities already developed, you will likely develop what is called quiet ADD or mixed ADD. If you are twelve, fifteen, eighteen months old, however, when this process begins, you will have barely begun to develop cognitive, language, and social skills and you will wind up with what has been called Autism/PDD.

The good news is that this concept is supported by common sense medical logic. The bad news is that we must unify and focus efforts or we will continue to see more adults that are supposed to be paying taxes and earning a living, finding themselves on welfare, unable to function, unable to produce. Even graver is that if nothing changes, we are currently raising an entire generation of children to this fate.

There is hope. Research from many prominent institutions support the idea that the brain is pliable at least into adolescence, maybe into early adulthood. It has been my rewarding experience as a pediatrician to see five, eight, ten, and even a twelve year old boy who could not talk, begin to use language. Parents who were told their child would never be independent, never be able to earn a living, and who one day might have to be placed in an institution, have seen their children become top of their class academically. I have children within the practice scoring in the 97th, even the 99th percentile on California and Illinois state testing.

The potential multiple triggers for this illness, we are calling NIDS, will need many, many years of ongoing research to learn how multiple factors such as stress, viral, or environmental may play a role. The key is to focus treatment efforts, rapidly, effectively – NOW – to keep from losing an entire generation of children while the ultimate "answers" are still being investigated. We can use technology to accurately define "subgroups" of these children and adults now, setting up the possibility of new therapy approaches in as little as the next 6 – 8 months, rather than after years of further investigation and study. Technology exists to help these children and to help many of the adults out there to become productive individuals again. At this time, as noted in the enclosed articles, I have been using a combination of diet elimination, anti-viral therapy, anti-fungal therapy, and application of low-dose SSRI's (Selective Serotonin Re-uptake Inhibitors), based on our NeuroSPECT findings, immune markers, and viral titers in these children. Thankfully, I have had many children return to normal and above-normal functioning, but this is not yet fast enough, simple enough, or perfect enough. This may be a holding approach thus far wherein balancing the many neurological immune regulating proteins known as cytokines and chemokines may in turn rebalance behavior itself. As many others are noting, I would propose there is a future for logical application of "alternative" medicines and combination treatment protocols with good pharmaceutically pure agents and medications.

In 1996, I was a speaker at the Autism Society of America Conference. Approximately 2000 parents and professionals gathered for this event. My wife, milling around, questioned me "Where are the doctors? The M.D.'s?" Sadly she had figured out the truth in a matter of minutes. The medical community had abandoned these children once they became labeled as "Autistic." These children were regarded as defective, mentally un-trainable, even retarded!

Sadly, with the label of autism, many children were not even given a simple blood test for anemia/iron deficiency (a simply-counteracted, possible cause of brain dysfunction). Reviewing case after case of children labeled as having Autism/PDD, I am horrified at how little has been done medically for these children, as they are not considered to be "normal." Their pain, their misery, their "illness," goes essentially unrecognized. Many are though of as insensitive to pain, but how many are actually just "numb" to the pain that their brain/system is constantly in? Simple steps that could be taken, are not taken to help these children or their parents.

I have been fortunate to work with Dr Israel Mena and Dr. Bruce Miller, who helped show through NeuroSPECT Scans, that these children had a physiological dysfunction going on in their brains. For the majority, there was a decrease in blood flow and function of the temporal lobe of the brain consistent with that predicted by neuro anatomists. I have many, many more scans that show the same decrease in blood flow. I would shudder to think of what dysfunctions you might have if your brain had lack of blood flow in those areas. In fact, if one listens to an adult with Chronic Fatigue Syndrome, or the "typing" of a child unable speak, one can only begin to imagine how truly horrible this is.

Many of these children have a low number of Natural Killer (NK) cells, which are a more primitive immune system cell, responsible for clearing "radicals" in our body, clearing foreign cells / cancerous cells, and considered a strong marker for a healthy or stressed immune system. These cells, when low in number, are now linked to viral reactivation in many auto-immune illnesses, and low NK cells has become an extremely strong marker in a subgroup of these children with NIDS.

Another frequent finding is the likely presence of an active HHV-6 virus (a human herpes virus) or other related Herpes viruses in these children. Similar findings are also being reported for various adult auto-immune disorders and recently even the Center for Disease Control published an article focusing on our emerging knowledge of HHV-6 related disorders.

The issue of vaccines is an important one. Again, one must understand the problem in terms of the new altered immune state (part of the bigger picture), rather than necessarily the vaccines themselves. Most doctors would agree that not vaccinating in this country would be a disaster. As I remember the Academy of Pediatrics and the fights in the 70's over the DPT vaccine, in the end the statistics of children supposedly damaged by the vaccine were no more then the "natural" incidence in life or 1 in 300,000. In fact in England and Japan, where for a time the DPT vaccine was stopped, the incidence of pertussis (whooping cough) resulting in serious illness and death, far exceeded any possible "vaccine connection." Likewise, in discussing the current "Autistic" / NIDS epidemic, while there may be a possible "triggering" factor with Rubella, Measles, "multiple" vaccines, one must understand this as only one of a possible combination of stresses causing dysfunction, within the concept of a preexisting "immune reactive" or "stressed" state. Vaccines (by themselves) remain an unlikely cause of Autism.

BUT injecting common sense, general awareness of health and appropriate "past" considerations of separations of vaccines, "stresses", choice of age, etc might save untold children potential reactions/disasters. Consistent with the question of whether there is a peculiar or unusual immune reactivity when a child is younger, waiting till a child is 3 or 4 could not be faulted, but with ongoing measles outbreaks occurring at times, it is not something easy to recommend routinely at this time. Infancy unfortunately represents a child's most vulnerable time to measles (but there is no real risk from rubella or mumps at that age).

Any injury or loss of a child that could have been prevented remains unacceptable. There is no way to adequately console the parent of a lost or damaged child. If "focused" correctly, we do have the ability to accelerate understanding and identification of potentially higher risk children. That would help immensely in considering the risks versus the gains of modifying vaccination schedules, diet advice, treatment choices, etc. We must work together with organized medicine and the pharmaceutical companies as allies to solve these questions, not as" adversaries, fighting to defend principles, which in the end we all believe in.

It has been my personal experience within the practice to literally have "high risk" children with "one foot in, one foot out" of the NIDS disorder, and prevent it from becoming full-blown Neuro immune dysfunction solely through use of "preventative" pediatrics. Via dietary eliminations, selective usage of antihistamines, "bacteriostatic" antibiotics (when indicated), aggressive allergy prevention and "health maintenance" providing a simple, preventative program to a seemingly-increasing number of families with high-risk factors for NIDS. While only an anecdotal observation, to date, NO family with whom I have instituted a preventative program for NIDS has had another "autistic spectrum" disorder child.

The bottom line is that these children have a disease, open to fascinating research on all its potential causes and triggers, but one that currently warrants and deserves immediate medical intervention. In my clinical practice, "miracles" seem to be happening routinely. One must realize, recoveries and significant cognitive improvements could not happen IF these children were truly born "defective" - thankfully, they were not. I have an increasing number of children who have been with me 2 or 3 years now and as they return to their regular pediatricians for their annual checkup, their pediatricians are seeing the children growing better and developing better, motor, body and brain wise. In a nice manner, while still not understanding this process (but smiling at the child they see before them), these pediatricians are advising the parents to continue therapy, as I continue to monitor medications appropriately.

A child I began treating at five is now in sixth grade, getting straight A's, was the Vice-President of his 5th grade class – not how most people view an autistic child. I have an increasingly large number of these children where "academics" are the least of anyone's worries for the child. Many are in regular if not honors classes and many are happy, well adjusted, indistinguishable from their peers. In reality these children are likely just the opposite of what this country and the world of medicine had come to think of them: as retarded, unable to develop fully, with some hope of compensation, but not real treatment or recovery (for one can not recover from a developmental disorder). Recovery and improvement in my patients, as previously mentioned and as explained in the attached articles, has been accomplished through a combined program of dietary elimination, anti-virals, anti-fungals, and low dose SSRI's. I have attempted to do this following good pediatric principles, while "combining" steps/therapies based on the emerging science of "Neuro-immune."

This past week a mom came in and told me her 5 yr. old child (who has been with me about 8 months now), said to her, "Mom do you want to pretend I can't talk? REMEMBER when I couldn't talk?" We have so misunderstood and misjudged these children. What harm are we doing to these children as a result?

If we can channel the technology that we have today and employ immune modulating agents, we could begin objective testing of new therapy protocols in as little as 6 – 8 months, with one (or more) related agents. Immune modulators, will give us the tools to regulate the Neuro-immune system as has never before been possible, help to create a "normal," essentially healthy state. A healthy immune system has the potential to "normalize" brain function, enabling the brain to turn back on and begin developing again.

If we can focus a unified effort to identify the specific immune markers (e.g. low natural killer cells, high alpha interferon's, high or low cytokine / chemokine profiles) that will let us understand which patient is the most likely candidate for which immune agent, separate this "mixed" population of children into logical subgroups, allowing more rapid understanding of vaccine or other potential related factors, and if we can proceed with the linking of a country wide, potentially world wide network of NeuroSPECT centers, to our already existing database of NeuroSPECT scans, the immediate pay-off will be to have a chance at saving this generation of children.

There is good, solid science in the NIDS Hypothesis. It has been reviewed and verified by at least four pharmaceutical companies to date. We need to see the urgency of this situation: we are already spending approximately 13 billion dollars annually on Autism and related disorders and this figure is projected to be significantly more in the near future. In reality, if treated young enough, most of these children could still become healthy, productive members of society, with full, rich lives of their own. I would dare say, many of these "Autistic" children are in reality supposed to be this country's "future" leaders, having starting off with that capability and background, and not as "defective" children (as had been previously thought). With the reported 263% increased incidence of autism in California, and a 500% increase in Florida, among other statistics, I cannot emphasize enough that we are truly losing a generation of children.

What may have often been presented to you as impossible or can't happen, in reality, can happen, but to occur, we must approach this as it's never been done before. In the normal course of medicine, with multi-million dollars of research, this is a slow evolution that will take an estimated five, ten years or longer to come together, to even begin to think of how can we treat this and deal with it. Within the NIDS Institute, our researchers, who are all heavily-credentialed, many are involved in current NIH and other activities and, with the NIDS Hypothesis, there is logic that says we can take this knowledge, these abilities, unify other researchers in institutions across the country, using technology, instead of being limited to colleagues or materials available within a given institution. We can literally pick-and-choose top people around this country, around this world to focus on this as the true crisis it has become. With that ability, we can look at applying these new therapies, new agents, within the next six months to a year at most. Instead of thinking about what are we going to do for the future, we can change this now.

I plead with you, Mr. Chairman and members of this Committee. These children are supposed to be a productive part of our country's future, not a health cost and burden. These children have the potential for full, productive, intelligent lives; contrary to the old idea, their genetics are not the determining factor. A child can NOT develop normally, develop some language and lose it all except in a disease process. We can apply good sound science and logic to help solve this crisis NOW. Unless we act NOW, we will continue to lose this generation of affected children, and will potentially watch the "bankrupting" of our current education and social system. Today's ill children cannot wait for the "normal" path of academic science to catch up (it has begun to move in the right direction, but all too slowly). We must leap forward in a way/model never done in medicine before. I am extremely fortunate to have three healthy children and one grandchild. I selfishly want the rest of my future grandchildren, all of yours and others out there, to have the same chance.

Thank you.

Michael J. Goldberg, M.D., F.A.A.P.

NIDS RESEARCH INSTITUTE

Sponsored by MAT: Medicine for Autism Today

Business Plan
Executive Summary

The Mission

The mission of the Neuro-Immune Dysfunction Syndromes (NIDS) Research Institute is to facilitate autism research and expeditiously identify effective medical treatment options for children with autism and other related neuro-immune and/or auto-immune conditions through the development of various private and public partnerships.

The Challenge

Autism affects over one-half million individuals and therefore is more prevalent than Cystic Fibrosis (30,000), Down's Syndrome (250,000), Multiple Sclerosis (350,000) and pediatric rheumatoid arthritis (50,000). However, the funding for research into cures for these conditions is up to ten (10) times greater than that of autism, which receives less than $20 of research funding per individual. This inequity is due primarily to an emphasis on behavioral diagnostic and treatment tools in lieu of the development of a scientific/medical model for autism treatment.

Moreover, the incidence of autism has exploded over the last decade and now occurs in at least 40 births per 10,000 (compared to 1-2 births per 10,000 only a decade ago). NIDS' demographic analysis also shows that special needs classifications like autism, ADD and speech and language disorders are increasing three times faster than the general population for children ages 5-19. Developmental disorders do not increase at these rates!!! **Thus, the only plausible explanation for such data is a medical disease process triggered by a combination of factors, including the environment.**

In addition, only one medical agent is under formal FDA review for the treatment of autism compared to 44 for childhood cancer, 14 for cystic fibrosis, nine for epilepsy and three for rheumatoid arthritis. NIDS wants to close these research gaps and provide our children with the future they deserve.

The Hypothesis

The NIDS Medical Board has developed a Clinical Hypothesis Statement (available upon request and through the NIDS website at *nids.net*) with over 60 peer reviewed journal references to support its research mission. The fundamental premise of the hypothesis is that these children are suffering from a dysfunctional relationship between the immune and neurological systems and require immune modulation to restore their cognitive potential. In addition, the following medical studies have been published in peer reviewed journals since the development of the Clinical Hypothesis Statement that further support the presence of neuro-immune and/or autoimmune dysfunction in children with autism:

- In the June, 1999 issue of the Journal of Pediatrics, a group of six researchers concluded that "the presence of (brain autoantibodies) raises the possibility that autoimmuity plays a role in the pathogenesis of language and social development abnormalities in a subset of children (with autism and LKS)". (*J Pediatrics* 1999; 134:607-613)
- In the June, 1999 issue of the Journal of Child Neurology, researchers led by Dr. Anne M. Comi of the Johns Hopkins Hospital in Baltimore, Maryland concluded that "autism appears to be more common in families with a history of autoimmune disorders". The study included 61 autistic patients and 46 "healthy" patients. (*J Child Neurology* 1999;14:388-394)
- In the September, 1999 issue of the Journal of Pediatric Neurology, Hornig et al presented an infection-based model of neurodevelopmental damage. In this study, a Borna disease virus resulted in behaviors such as hyperactivity, inhibition of open-field exploration and stereotypic behaviors. The resemblance of these functional and neuropathological abnormalities to human neurodevelopmental disorders suggests that this model may have utility for defining the biochemical and functional outcomes of interactions of environmental influences with the developing central nervous system. (*J Pediatr Neurol* 1999; 21(3):619-21)
- Physicians at Memorial Sloan Kettering in New York reported in the *New England Journal of Medicine* this year that men with testicular cancer and brain damage had a particular type of antibody in their blood that may have caused the brain damage. They believe the brain damage was not caused by the cancer, but by an overly aggressive attack by the body's own immune system on a protein produced by tumors. This is the third study to link brain damage to an immune system attack on cancer.

The Plan

To this end, the NIDS Research Institute has developed a business plan that will attempt to expedite the research process on behalf of these children in an unprecedented fashion. This will be accomplished by developing the necessary clinical focus through the medical board, developing partnerships with private funding resources for our short-term financial needs ($750,000) and ultimately integrating public funding and research resources for the long-term needs ($5 to $10 million and government-sponsored research). The short-term tactical plan is as follows:

- Develop a clinical database (with appropriate control subjects) that evaluates the medical aspects of autism, including any immune system dysregulation that may contribute to the symptoms seen in autism ($150,000)

- Identify clinical sub-groups of children with autism based on the immune system factors catalogued in the medical database to more accurately target the types of agents for review (included in database development costs)

- Conduct animal trials with the agents that offer the most potential to evaluate and maximize patient safety during clinical trials ($125,000)

  NOTE: Animal trials have been conducted within FDA standards for adults. Additional studies *may* be necessary prior to child trials.

- Conduct trials of immune modulators on adult patients with NIDS conditions to evaluate their efficacy and confirm that these patients present similar immune profiles to those of children with autism ($150,000)

- Secure the licensing rights to multiple immune system agents, including neuropeptides such as VIP and Peptide T, that have the potential to remediate the disease process in a defined sub-set of children with autism

- Develop a network of research sites (which include NeuroSPECT brain imaging capabilities) to facilitate the review of these agents. Sites will likely include UCLA, UMDNJ in New Jersey, University of Miami and a medical facility in Sydney, Australia ($250,000)

- Present the data and research noted above to the pharmaceutical industry and commission interested parties to facilitate FDA approved clinical trials that comply with all federal safety and efficacy guidelines ($75,000)

  NOTE: Glaxo-Wellcome, Smith Kline Beecham, Advanced ImmunoT and Roche have each requested additional information as outlined above.

The NIDS Research Institute believes that execution of this short-term tactical plan will position it to change the course of treatment for NIDS patients and ultimately improve the health of this population.

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NIDS

N.I.D.S

THE NIDS MEDICAL ADVISORY BOARD PRESENTS:

A DRAFT PROPOSAL OF ITS NEURO-IMMUNOLOGY HYPOTHESIS STATEMENT CONCERNING AUTISM

Clinical Hypothesis - Immune "Dysfunction / Dysregulation" - A Reason for Childhood Neuro-Cognitive Dysfunction:

Autism, as classically defined, is a devastating *disorder* that often robs children of their ability to communicate and thrive in society. It is characterized by primary alterations in social interactions and receptive/expressive language, and is often accompanied by symptoms including ritualistic behaviors and a lack of imaginative play. Additionally, many "autistic" children exhibit a craving for sensory (vestibular) stimulation that often manifests itself in self-stimulatory behaviors (e.g., spinning and hand-flapping).

By definition, autism has an early onset before 30 months of age (which has now been extended to 36 months under the DSM-IV guidelines), while disorders appearing later in life have been thought to be symptomatically and medically different from "autistic" conditions. However, publications over the last 13 years have cast some doubt on this assumption, and it has been noted in the literature that there is no firm evidence that similar or identical syndromes might not develop in older children.[1]

From an epidemiological standpoint, autism has migrated from a rare disorder to one that is now ten (10) to twenty (20) times more likely to be diagnosed. Ten years ago, "autism" occurred in 1-3 per 10,000 births. Now, current estimates suggest an incidence rate of 20 – 40 per 10,000 births. In fact, "cluster groups" throughout the world are currently being analyzed due to even higher incidence rates. It is also worth noting that other neuro-cognitive conditions such as "quiet" ADHD and "mixed" ADHD have received a renewed focus and attention among children and adolescents due to their perceived increase in incidence rates. Although a portion of these increases can likely be attributed to better and earlier recognition by the medical community and parents, the NIDS Board believes that this increase must prompt a change in how we approach these children. Specifically, we must begin to consider that these are not congenital,

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brain-damaged conditions but instead are medical disease processes acquired early in life.

In accordance with this premise, recent discussions have focused on the differentiation between **"congenital autism"** (including "classic" Kanner autism) and another form related to neurologic and medical disorders such as tuberous sclerosis, phenylketonuria, congenital rubella, and Down's syndrome. However, a third form has emerged which is being referred to as **"acquired or regressive autism"** (perhaps the largest sub-group of these children). For purposes of this hypothesis statement, "acquired autism" is a condition in which the child develops normally for the first 12 to 18 months of life and then regresses into the increasingly wide spectrum of "autistic" disorders.

These children challenge the previous belief that 70% to 80% of autistic children are mentally retarded. They crawl, sit up, walk, and usually attain "normal" motor milestones on schedule. Until the age of symptom onset, they are affectionate and appear to have above average intelligence. Children with acquired autism may begin to develop some speech but then, without warning, cease to progress, and begin to regress. Suddenly, these children become withdrawn. They vacillate between being quiet and hyperactive. Often self-stimulatory behaviors (i.e. arm flapping, rocking, spinning, or head banging) may develop. Over time, some manifest symptoms that are both similar and atypical of children previously diagnosed as having congenital autism. **The authors propose that many of these children with acquired autism fall into the medical category of N.I.D.S. (Neuro-Immune Dysfunction Syndromes), and need to be viewed as suffering from an auto-immune medical illness that is potentially treatable.**

The Past:

Unfortunately, without the tools or the technology to accurately investigate the human brain, the label of "autism" evolved as a set of symptoms in a young, dysfunctional child. In its most severe form ("classic autism"), effective speech was absent and clinicians often saw symptoms of repetitive, highly unusual, aggressive and sometimes self-injurious behavior. Those afflicted had extremely abnormal ways of relating to people, objects, or events. Parents noticed that something was "not right," often within the first three to six months of life. These children typically did not smile and often resisted affection.

Most researchers and clinicians did not look for "medical" answers to autism because they believed it was a disorder that was medically untreatable. Without the technology to understand these children, pediatricians and pediatric psychologists accepted the concepts of poor parenting, childhood psychosis/schizophrenia and classified "autism" as a psychological and/or developmental disorder. Treatment was typically delivered by psychologists and psychiatrists.

Eventually, it became well documented that known medical disorders such as tuberous sclerosis, PKU, congenital rubella, and others could cause autism. However, to date, these remain rare disorders and a small sub-group of autism. Given that researchers are just now beginning to understand the medical origins and implications of the potential therapies for these children, autism is still treated primarily by psychologists and educators (with mixed results).

Past Medical Research:

A review of the existing medical literature relative to autism research reveals evidence of an emerging *medical disease process* in these children. For instance, research indicates that autism can follow infectious disorders affecting the central nervous system including encephalitis.[2,3,4,5] Multiple studies have focused on various anatomic locations of suspected dysfunction.[6,7,8,9] It is important to note that emphasis is often put on the *medial temporal lobe*. Pertinent to this new "model" of dysfunction, are the multiple published reports of autistic symptoms developing in association with encephalitis in children. (Ref: 1981 DeLong[10], 1986, Gillberg,[11] 1989,[12]) Most of these reports site injury to the temporal lobes as part of their findings. This is consistent with the areas of decreased function identified on NeuroSPECT scans initially by Dr. Ismael Mena from the NIDS Board and now by Dr. Bruce Miller and Dr. Fred Mishkin, both of who have clinical research in progress.

New research techniques are increasing the rates at which Herpes Simplex Virus (HSV) sequences are being identified in temporal lobe tissues[13,14] (i.e., locales likely to be substrates for various aspects of autism). In 1975, an article was published in Cortex[15] describing a syndrome similar to autism in adult psychiatry. The condition involves the loss of emotional significance of objects, the inability to adapt in social settings, the loss of recognition of the significance of persons, and the absence of sustained purposeful activity *after temporal lobe damage*.

The literature also comments on the cognitive and behavioral deficits caused by temporal lobe damage in Herpes encephalitis. There are many reports, particularly in the British literature,[16] suggesting a connection to coxsackie/enteroviruses, while in the United States it has been suggested that many cases may be linked to the Herpes family of viruses (i.e., EBV, HHV6, HHV7, CMV, etc.).[17,18,19,20,21] Neither theory has been conclusively proven, nor has the evidence for a contagious disorder been conclusive (although some have inferred it based upon incidents related to epidemic outbreaks[22,23]) However, HSV in humans has long been known to prefer temporal lobe and limbic sites. One theory focuses on the olfactory nerves as a possible route for infection, but oral cavities may also provide entry. In 1996, O'Meara et al postulated that: "Inoculation of murine tooth pulp with HSV selectively infected the mandibular division of the trigeminal

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nerve and caused encephalitis predominantly affecting the temporal cortex and limbic system, a pattern of disease similar to human HSE [herpes simplex encephalitis]...[24]."

While other studies have also implicated the temporal lobes in the pathogenesis of autism,[25,26] a direct association between temporal lobe pathology and autism has not yet been proven conclusively. In fact, research has found a variety of lesions in the "autistic" brain, particularly in the cerebellum.[27] These variable findings may be due to the heterogeneity (differences) in the possible etiologies or time/duration effects within this syndrome.

Although Herpes virus has a predilection for the temporal lobes,[28] the course of autism does not suggest an acute infection with traditional Herpes viruses. [29] However, delayed temporal lobe development early in life may produce different symptoms from those arising from deterioration or destruction of previously normal lobes.

In summary, although not conclusive, past research further strengthens the linkage of the temporal lobe and "autistic" symptoms. Boucher and Warrington noted similarities between behavioral deficits reported in animals with hippocampal lesions and autistic behavior.[30] Medial temporal lobe damage on pneumoencephalograms was reported in a subset of autistic children.[31] Damasio and Mauer proposed that "the syndrome results from dysfunction in a system of bilateral neural structures that includes the ring of mesolimbic cortex located in the mesial frontal and temporal lobes, the neostriatum, and the anterior and medial nuclear groups of the thalamus. At least two other studies have also implicated the temporal lobes in the pathogenesis of autism.[32,33]

The Present:

With new and more precise tools and technology available to us now, the medical anatomy of "autism" is gaining definition after years of conflicting findings. Currently, EEG abnormalities[34], immune markers, and NeuroSPECT findings support the concept of a *medical disease process* occurring in these children's brains. For example, it is generally recognized that an EEG finding of "slow" waves or "abnormal" brain wave activity is often consistent with the idea of an underlying and unknown "encephalopathy/encephalitis."

In addition, recent work with the NeuroSPECT strengthens the connection of blood flow abnormalities and neuro-dysfunctional states, particularly in situations in which patients appear to have immune and/or possible viral etiologies. NeuroSPECT scans capture blood flow through specific areas of the brain. Blood flow correlates with function/activity.[35,36] As noted, NeuroSPECT scans on children with autism have shown a decrease in blood flow in the temporal and parietal areas, which is consistent with past reports of temporal lobe dysfunction in such children. Neurological models of the brain correlate right temporal lobe areas with social skills and left temporal lobe areas with speech and auditory dysfunction, all of which are compromised in autistic children. It

should also be noted that there is no good explanation for our finding of increased blood flow in the *frontal lobes* of a group of these children, which is more consistent with ADD and Hyperactivity. Further research is required relative to this finding.
Also, the Board has been monitoring the emerging body of evidence related to the immune system and its interactive messengers: interleukins and cytokines. It appears that a dysregulated immune system state, whether triggered by a virus, genetic disposition, intrauterine, prenatal, neonatal stress or trauma, may account for the cognitive processing and other deficits seen in some children with autism. This concept is supported by the lack of consistent neurological/anatomical abnormalities and metabolic abnormalities in these children. We now know that neuro-polypeptides called cytokines can and do restrict brain blood flow under certain conditions. In these children, we may be looking at an immune system continually sending out signals to restrict brain blood flow. Whether this continues as an "auto-immune" reaction (whereby the immune system continues this pathway with no active reason to do so) or is due to the presence of a retro-viral or other viral process is open to further research. However, the concept of an immune-related disease process in a large number of these children appears unquestionable at this point in time.

Futhermore, many autistic children have major allergies or intolerances to many chemicals and foods. While occasionally these reactions may turn into urticaria or asthma, the effect in the majority of these children is the worsening of autistic-like behavior. Family history often reveals eczema, migraines (especially in mothers) hay fever, asthma, and histories of other disorders, which are often immune-mediated. These external symptoms may well prove to be signs of a "hyper-reactive" / stressed / dysfunctional immune system underlying the biochemistry of these children. Many anecdotal reports of successful therapies for autistic children (e.g., gammaglobulin, allergy-free diets) can most likely be explained through the concept of regulating a dysfunctional immune system and/or altering metabolic sensitivities and dysfunction.

Examples of autism's probable connection to immune dysfunctional states are:

Extensive clinical work over the last four to five years further supports the Board's hypothesis that we are facing an immune-mediated disease state affecting the central nervous system (CNS) in these children. The literature is replete with articles connecting immune system abnormalities to autism, ADD, ADHD, CFS and CFIDS. Among the main examples are:

1. Multiple researchers have found evidence that autoimmunity is a possible mechanism to explain autistic symptoms.[37,38,39,40,41]
2. An increased incidence of two or more miscarriages and infertility[42] as well as pre-eclampsia[43] and bleeding during pregnancy[44] have been shown to occur in mothers of autistic children. There are also multiple studies in the obstetrical literature connecting these events to immune autoantibody production.

3. Studies have been done comparing the maternal antibodies of mothers with their autistic children,[45] suggesting an association of abnormal maternal immunity with autism. Antibodies reactive with lymphocytes of fathers of autistic children have also been found.

1. Multiple researchers have shown an interaction of maternal antibodies with trophoblast or embryonic tissue antigens, and a cross-reaction with antigens found on lymphocytes.[46,47,48,49]
2. Researchers have also shown a significant depression of CD4+ T helper cells and their suppresser-inducer subset[50-51] with an increased frequency of the null allele at the complement C4B locus[52] in children with autism. As similar changes have been known to occur in other autoimmune diseases,[53,54] these researchers have postulated that immune activation of a T-cell subpopulation may be important in the etiology of the disorder in some children with autism. (Note: Many of the autistic children evaluated by the Board have shown very high CD4 and CD8 counts, low natural killer (NK) cells, or other "markers" consistent with immune dysfunction/ dysregulation).
3. Abnormalities of Cell Adhesion Molecules (NCAM) [55] have been reported.
4. Antibodies to neurofilament axonal proteins (NFAP) have been noted in autistic children [56a] and have been reported in neurotropic slow virus diseases (Kuru and Creutzfeld-Jacob disease) in adults.[56] Other studies[57,58] have suggested an association of an infectious agent (slow virus) in the etiology of these diseases. This is considered indirect evidence that some cases of autism may also be associated with the concept of a "slow virus."
5. Anti-central nervous system serum immunoglobin reactivity has been reported that was specifically directed against the cerebellum. [56a]
6. A small percentage of autistic children with demonstrable immunologic abnormalities have normalized their autistic symptoms with intravenous immunoglobulin treatment. [58a] [58b] This result shows that immune abnormalities can cause autism in a subset of children and that "acquired autism" can be effectively treated.
7. Singh et al. hypothesized that autoimmunity secondary to a virus infection may best explain autism in some children.[59] Congenital rubella virus[60] and congenital cytomegalovirus[61] have been indirectly involved as causative factors in autism.

Given this support from the medical research literature, the concept of immune dysregulation as a medical disease process in childhood neuro-cognitive dysfunction is an emerging reality. This concept could easily account for a portion of the increase of neuro-cognitive diagnoses over the last ten years. Whether the etiology of this dysfunction is related to environmental factors (e.g., ozone layer depletion, local toxins, etc.), new retro-viruses, stealth, spongiform or

other viruses (or altered viral responses), we now have a medical hypothesis that can facilitate the definition of clinical sub-groups and lead to the treatment of these patients without first determining the origin or etiology.

If an infectious etiology indeed exists, it may be as ordinary as the common cold, or so rare that we have not yet developed the tools to either identify or study it. Whether an ongoing agent is present, or the body simply remains in a dysfunctional state, it seems likely we are confronted with a phenomenon/illness that has multiple etiologies, multiple origins, and various clinical manifestations. At this point, they appear linked by an immune dysfunction or possible viral-mediated state. Genetic predisposition to this syndrome may have a great deal to do with why certain individuals suffer with these symptoms. However, we must begin to consider these apparently heterogeneous expressions as linked and potentially treatable through the common pathway of an immune dysfunctional/CNS dysregulated state. For example, in a recent study[62] on Chronic Fatigue Syndrome (CFS), two NIDS Board members reported a significant diminution of blood flow in both the temporal and, to a lesser degree, the parietal lobes in children suffering from CFS and Chronic Fatigue Immune Dysfunction Syndrome (CFIDS). These findings are similar to those previously noted in children with acquired autism.

Based on the evidence presented herein, the NIDS Board believes that developing a focus on the inter-relationship of autism, ADD, ADHD, CFS, CFIDS and other immune-modulated conditions is a key to helping groups of these children in ways never before possible. If we can address the physiologic part of the dysfunction in these children (irrespective of its specific etiology), educational therapy, counseling, study techniques and most/all other current therapies have a far greater probability of success. In addition, research focused on developing and initiating new therapies for autism are likely to be useful in treating these other inter-related childhood disorders.

The Future:

As outlined, we have witnessed the evolution of what is now being recognized and accepted at the National Institutes of Health (NIH), the Centers for Disease Control (CDC), and academic institutions world-wide as a "neuro-immune" epiphenomena. Studies are now confirming the concept of physiologic immune-mediated diseases underlying an abnormal physiologic state for these patients. This, in turn, creates both physical and neuro-cognitive deficits and dysfunction, usually of long-term duration.

The NIDS Board believes that many of the characteristics ascribed to autistic (and "quiet" ADHD) children overlap with the multiple complaints of adults afflicted with components of CFS/CFIDS and adult "ADHD". As previously noted, all of these groups have reports of various immune abnormalities including T-cell changes reflected, for example, by increased or decreased CD4/CD8 cells, increased / decreased NK and B cells, and altered viral titers. It is this common denominator of immune alterations that gives hope for potential new therapies in the near future for these children.

However, while this hypothesis now has support in the literature, there are many important questions to be answered. How many "autistic" children have evidence of or are linked to an immune-dysfunctional state or a conclusive viral etiology? Can these children be viewed and treated differently than the "classic autistic" child of 20 to 30 years ago? Is their prognosis for recovery significantly better than the "classic autistic" children from the past?

It is time to recognize that these children are likely suffering from a medical disease process and need our clinical and research efforts now! Current treatments need to be modified and adjusted to account for this finding. The symptoms of the "quiet" ADD child (who is likely connected to this phenomenon) is not consistent with the past training or processes used to "explain" and address the "hyper" ADD child. It seems likely that the cognitive defects described in adults and children with CFIDS may be thought of as milder, later-onset form of "autism", as they are similar in symptomatology and possible etiologies. The continued exploration of an immune-dysfunctional epiphenomena, and the potential etiologies linked to it, is a door we must walk through if we expect to change the future of this generation of children!

It is the proposed mission of this Board to accelerate the integration of the above clinical and research findings to facilitate the employment of new (and perhaps some older) immune-modulating therapies in the treatment of "acquired autism", ADD/ADHD and CFS/CFIDS. We believe that by helping to "regulate" or "normalize" the immune system, we can restore health to these children. Through our unique acceleration of clinical knowledge and academic research, there is a chance to recognize and treat this disease process while these children are still young and while there is still time to effectively help their cognitive development.

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1 Waterhouse, L., Fein, D., Nath, J., & Snyder, D. (1984). Pervasive schizophrenia occurring in childhood: A review of critical commentary. In American Psychiatric Association, Diagnostic and statistical manual of mental disorders(DSM-III): An interim appraisal. Washington, D.C.:

2 Delong, G.R., Bean, S.C., & Brown, F.R.,III.(1981). Acquired reversible autistic syndrome in acute encephalopathic illness in children. Archives of Neurology, 38, 191,194

3 Gillberg, C.(1986). Brief report: Onset at age 14 of a typical autistic syndrome. A case report of a girl with herpes simplex encephalitis. Journal of Autism and Developmental Disorders, 16,369-375

4 Greer, M. K., Lyons-Crews, M., Mauldin, L.B. & Brown, F. R. III. (1989). A case study of the cognitive and behavioral deficits of temporal lobe damage in herpes simplex encephalitis. Journal of Autism and Developmental Disorders, 19, 317-326

5 Plioplys, A.V., Greaves, A., Yoshida, W.: Anti-CNS antibodies in childhood neurologic diseases. Neuropediatrics 20: 93-102, 1989.

6 Boucher J., Warrington EK: Memory deficits in early infantile autism: Some similarities to the amnesic syndrome. BR J. Psychol 1976;67:76-87

7 Hauser S.L., DeLong G.R., Rosman N.P.: Pneumographic findings in the infantile autism syndrome: A correlation with temporal lobe disease. Brain 1975, 98:667-688

8 Damasio A.R., Maurer R.G.: A neurological model for childhood autism. Arch Neurol 1978;35;777-789

9 Courchesne, E. (1991). Neuroanatomic imaging in autism. Pediatrics, 87(Suppl.part 2), 781-890

10 DeLong G.R. et al. Acquired reversible autistic syndrome in acute encephalopathic illness in children. Arch Neurol 38.191-4 1981.

---

11 Gillberg, C. (1986). Brief report: Onset at age 14 of a typical autistic syndrome. A case report of a girl with herpes simplex encephalitis. Journal of Autism and Developmental Disorders, 16,369-375

12 Greer, M.K., Lyons-Crews, M., Mauldin, L.B. & Brown, F.R. III. (1989). A case study of the cognitive and behavioral deficits of temporal lobe damage in herpes simplex encephalitis. Journal of Autism and Developmental Disorders, 19, 317-326

13 Jay V. et al. Pathology of chronic herpes infection associated with seizure disorder... Ped Pathol Lab Med 15.131-46 1995.

14 Sanders V.J. et al. Presence of herpes simplex DNA in surgical tissue from human epileptic seizure foci detected by polymerase chain reaction. Arch Neurol 54.9554-60 1997.

15 Marlowe, W.B., Namcall, E.L., & Thomas, J.J. (1975). Complete Klüver-Bucy syndrome in man. Cortex, 11, 53-59

16 Behan P.O., Behan W.M.H, Bell E.J. The post-viral fatigue syndrome. J Infect Dis 1985;10:211-222

17 Borysiewicz L.K., Haworth S.J., Cohen J., Mundin J., Rickinson A., Sissons J.G.P. Epstein-Barr virus-specific immune defects in patients with persistent symptoms following infectious mononucleosis. Q J Med 1986;58:111-21

18 Jones J.F., Ray C.G., Minnich L.L., Hicks M.J., Kibler R., Locas D.O. Evidence of active Epstein-Barr virus infection in patients with persistant, unexplained illnesses: elevated anti-early antigen antigen antibodies. Ann Intern Med 1985;102:1-7

19 Kroenke K., Wood D.R., Mangelsdorff A.D., Meier N.J., Powell J.B. Chronic fatigue in primary care: prevalence, patient characteristics, and outcome. JAMA 1988;260:929-34

20 Holmes G.P., Kaplan J.E., Stewart J.A., Hunt B., Pinsky P.F., Schonberger L.B. A cluster of patients with a chronic mononucleosis-like syndrome: is Epstein-Barr virus the cause? JAMA 1987;257:2297-302

21 Krueger G.R.F., Koch B., Albashi D.V. Persistent fatigue and depression in patients with anti-body to human B-lymphotropic virus. Lancet. 1987;2:36

22 Jenkins R. Post - viral fatigue syndrome. Epidemiology: lessons from the past. Br Med Bull 1991 Oct ;47(4) : 952-65

23 Wallace P.G. Post - viral fatigue syndrome. Epidemiology: a critical review. Br Med Bull 1991 Oct ;47 (4) : 942 - 51

24 O'Meara M. et al. Viral encephalitis in children. Current Opinion in Pediatrics 8.11-15 1996.

25 Hetzler, B., & Griffin, J.(1981). Infantile autism and the temporal lobe of the brain. Journal of Autism and Developmental Disorders, 11, 317-330

26 Jones, P.B., & Kerwin, R.W. (1990). Left temporal lobe damage in Asperger's syndrome. British Journal of Psychiatry, 156, 570-572

27 Courchesne, E. (1991). Neuro-anatomic imaging in autism. Pediatrics, 87(Suppl. part 2), 781-890

28 Greer, M.K., Lyons-Crews, M., Mauldin, L.B. & Brown, F.R. III. (1989). A case study of the cognitive and behavioral deficits of

temporal lobe damage in herpes simplex encephalitis. Journal of Autism and Developmental Disorders, 19, 317-326

29 Ghaziuddin, M. Tsai, L.Y., Eilers, L. & Ghaziuddin N. Brief Report: Autism and Herpes Simplex Encephalitis. Journal of Autism and Developmental Disorders, Vol. 22, No. 1,1992

30 Boucher J., Warrington EK: Memory deficits in early infantile autism: Some similarities to the amnesic syndrome. BR J Psychology 1976;67:76-87

31 Hauser S.L., DeLong G.R., Rosman N.P.: Pneumographic findings in the infantile autism syndrome: A correlation with temporal lobe disease. Brain 1975, 98:667-688

32 Hetzler, B., & Griffin, J.(1981). Infantile autism and the temporal lobe of the brain. Journal of Autism and Developmental Disorders, 11, 317-330

33 Jones, P.B., & Kerwin, R.W. (1990). Left temporal lobe damage in Asperger's syndrome. British Journal of Psychiatry, 156, 570-572

34 Plioplys, A.V. Autism: EEG abnormalities and clinical improvement with valproic acid. Arch. Pedlair. Adolesc. Med. 148:220-222, 1994.

35 Ichise M., Salit I.E., Abbey S.E., Chung D.G., Gray B., Kirsh J.C., Freedman M. Assessment of regional cerebral perfusion in 99 Tem-HMPAO SPECT in chronic fatigue syndrome. Nucl Med Comm 1992; 13: 767-772

36 Costa D.C., Brostoff J. Ell PJ. Brain stem hypoperfusion in patients with myalgic encephalomyelitis- chronic fatigue syndrome (abstract) Eur J Nucl Med 1992: 19(8): 733

37 Weizman, A. , Weizman, R., Szekely, G.A., Wijsenbeek, H., and Livni, E. , Abnormal immune response to brain tissue antigen in the syndrome of autism, Am. J. Psychiatry 7, 1462-1465, 1982

38 Todd, R.D., and Ciaranello, R.D., Demonstration of inter- and intraspecies differences in serotonin binding sites by antibodies from an autistic child, Proc. Natl. Acad. Sci. USA 82, 612-616,1985

39 Singh, V.K., Fudenberg, H.H., Emerson, D. and Coleman, M., Immunodiagnosis and immunotherapy in autistic children, Ann. N. Y. Acad. Sci. 540, 602-604, 1988

40 Plioplys, A.V.: Autism: immunologic investigations, in Gillberg, C. (ed): Diagnosis and Treatment of Autism, New York, Plenum Press, pp. 133-138, 1989.

41 Plioplys, A.V. Selective suppression of maternal IgG anti-central nervous system antibody reactivity. Developmental Brain Dysfunction. 7:165-170, 1994.

42 Funderburk, S.J., Carter, J., Tanguay, P., Freeman, B.J. & Westlake, J.R. (1983), Parental reproductive problems and gestational hormone exposure in autistic and schizophrenic children. J. Autism Dev. Disord., 13:325-332

43 Stubbs, E.G., Ritvo, E.R. and Mason-Brothers, A. (1985), Autism and shared paternal HLA antigens. J. Am. Acad. Child Adolesc. Psychiatry, 24:182-185

44 Peterson, M.R. & Torrey, E.F. (1976), Viruses and other infectious agents as behavioral teratogens. In: The Autistic Syndrome, ed. M. Coleman. New York: American Elsevier

---

45 Warren, R.P., Cole, P., Odell, D. et al. Detection of maternal antibodies in Infantile Autism. J. Am. Acad. Child Adolesc. Psychiatry, 1990,29, 6:873-877

46 McConnachie, P.R. & McIntyre, J.A. (1984), Maternal antipaternal immunity in couples predisposed to repeated pregnancy losses. AJRIM, 5:145-150

47 Faulk, W.P. & McIntyre, J.A. (1981), Trophoblast survival. Transplantation, 31:1-5

48 McIntyre, A. & Faulk, W.P. (1982), Allotypic trophoblast-lymphocyte cross reactive cell surface antigens. Hum. Immunol., 4:27-36

49 Plioplys, A.V., Greaves, A., Kazemi, K., Silverman, E. Lymphocyte function in autism and Rets syndrome. Neuropsychobiology 29: 12-16 1994.

50 Yonk, L.J., Warren, R.P., Burger, R. A., Cole, P., Odell, J.D., Warren, W.L., White, E., and Singh, V.K., CD4+ helper T cell depression in autism, Immunol. Lett. 25, 341 - 346, 1990

51 Warren, R.P., Yonk, L.J., Burger, R.A., Cole, P., Odell, J.D., Warren, W.L., White, E., and Singh, V.K., Deficiency of suppressor-induced (CD4+CD45RA+) T cells in autism, Immune. Invest. 19, 245-251, 1990.

52 Warren, R. P., Singh, V.K., Cole, P., Ode, JD, Pincer, CB, Warren, W.L., and White, E., Increased frequency of the null allele at the complement C4b locus in autism, Cline. Exp. Immune. 83, 438 - 440, 1991.

53 Morimoto, C., Rheinherz, E.L., Schlossman, S.F., Schur, P.H., Mills, J. A., and Steinberg, A.D., Alterations in immunoregulatory T cell subsets in active systemic lupus erthematosus, J. Clin. Invest. 66, 1171-1174, 1980.

54 Morimoto, C., Hafler, D.A., Weiner, H.L., Letvin, N.L., Hagan, M., Daley, J., and Schlossman, S.F., Selective loss of the suppressor-inducer T-cell subset in progressive multiple sclerosis: Analysis with anti-2H4 monoclonal antibody, N. Engl. J. Med. 316, 67-72, 1987.

55 Plioplys, A.V., Greaves, A., Kazemi, K., Silverman, E. Lymphocyte function in autism and Rets syndrome. Neuropsychobiology 29: 12-16 1994.

56a Plioplys, A.V., Greaves, A. Kazemi, K., Silverman, E. Immunologic reactivity in autism and Rett syndrome. Developmental Brain Dysfunction. 7:12-16, 1994.

56 Toh, G.H. et al. 1985. Proc Nat'l. Acad. Sci. USA 82: 3485

57 Galbraith, G.M.P. et al 1986 J. Clin. Invest. 78:865

58 Toh, G.H. et al. 1985. Proc Nat'l. Acad. Sci. USA 82: 3485

59a Plioplys, A.V. Intravenous immunoglobulin treatment of children with autism. Journal of Child Neurology. 13:79-82, 1998.

59b Plioplys, A.V. Treatment of autistic children with intravenous immunoglobulin. Journal of Child Neurology. 14:203-205, 1999.

---

59 Singh V.K., Warren R.P., Ode J.D., and Cole P. Changes of Soluble Interleukin - 2, Interleukin - 2 Receptor, T8 Antigen, and Interleukin - 1 in the Serum of Autistic Children. Clinical Immunology and Immunopathology 61, 448-455 (1991).

60 Chess, S., Autism in children with congenital rubella, J. Autism Childhood Schizophrenia 1, 33-47, 1971.

61 Stubbs, E.G., Ash, E. and Williams, P.S., Autism and congenital cytomegalovirus, J. Autism Dev. Disord. 14, 249-253, 1983.

62 Goldberg MJ, Mena I, Darcourt J. NeuroSPECT Findings in Children with Chronic Fatigue Syndrome. Journal of Chronic Fatigue Syndrome, Vol. 3,Num. 1 1997 61-67

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CFS/CFIDS
AUTISM

Winter, 2000

Autistic Spectrum Disorder / NIDS – Into the New Millennium: Science

SCIENCE says:

- An epidemic can NOT be due to a developmental or genetic disorder
    - ONE MUST have a ***disease*** process at work.
- The ONLY possible ***CAUSE*** for this type of disorder / dysfunction has become immune and / or viral in origin.
    - This was apparent as far back as a major research symposium October 1997 – since then basic science keeps supporting "neuro-immune" as the only logical pathway for most / all of these children.
        - The NIDS hypothesis has been validated by multiple reviewers to date
    - This IS not a metabolic disorder in origin – therefore metabolic "findings" are secondary not primary factors.
- Vaccines may be possible "triggers" but they are NOT the cause of this disorder / epidemic.
    - There is too much data over decades supporting the lack of "causation."
        - But, action as a potential "trigger" is open to scientific investigation (in some cases).
- New agents, working directly on the "neuro-immune" pathways (safest manner for children and adults) are possible now. Not by waiting for the science of "Autism" to catch up, but by applying to these children now what has thankfully been evolving "scientifically" in other fields to date.

As trials are about to get underway with new immune modulators for adults, we have a chance to help see children evaluated along with the adults, rather than years after. This has NEVER happened before, but can happen NOW, this year. BUT, as I have written and discussed, as has been always true, NO Company is going to "gamble" on investing potentially millions in new drug protocols, especially with children, UNLESS there is a hard, scientific process to make possible very "objective" data, for the FDA, etc. Thanks to the expertise represented in the NIDS Medical Board, this is possible NOW.

As new information emerges strengthening our understanding of the "neuro-immune system" and its influences, regulatory responses, feedback loops, etc., it has become logical and undeniable that this will ultimately be the route to understanding the key dysfunction in the children being labeled "Autistic Spectrum" (and many other cognitive dysfunctional states in children and adults). The only question is, will it be applied to help children now, or will the children (and their families) have to "wait" many more years till the "system" is ready. Unfortunately, under the normal evolution of science (even accelerated), our "system" is still many years away before thinking agents like this would be "ready" to be investigated "knowledgably" in these children. ONE day that will happen, it is inevitable, it has only become a question of how soon. Why not NOW?

Happily (or sadly depending upon what happens), the NIDS Board can help make this change and happen now, but continues to wait for funding and support to move ahead. The NIDS Board represents researches that have already been working in the field of "Neuro-immune" for the last 15 – 20 years, and together with the rapid application of solid science represent a chance to "leap frog" the "system" for your children. So, as we enter the new millennium, what's wrong?

At a recent research meeting I attended, it became obvious that we need to be able to reach out to groups like the American Academy of Pediatrics, hopefully help them wake up to the gravity of the situation, and then be able to get their support (and other groups in organized medicine) to deal with this as the crisis, the grave epidemic it has surely become. But instead we lose chances for their support, alienate them by "unscientific" allegations, and "convoluted" hypothesis being currently proposed by many autistic "experts." Do we want to spend years fighting "battles" that needn't be, that in the end are not going to be the "big picture" anyway. (Note: at this "mainstream" pediatric update conference were discussions of the "expanding" role of HHV6 disease in children and discussion about an "allergic – autoimmune encephalitis," topics that would never have been discussed even a few years ago.) In the coming years, there are going to be many fascinating "side" connections, new information and details to define, but the key now, is to focus on "therapy application," build upon what makes sense now, while we pursue these further details, not while we fight over them (due to many "false" accusations or assumptions), or prepare to study them (many good researchers are beginning to pursue many of the "pieces" of this puzzle), but would still wait to apply therapy till WE "understand" things further.

We need to focus behind the NIDS Medical Research Board as a path to trials with new agents within the next 6 – 8 months, not 10 years. Unfortunately, IF this fails, then it may well be 10 years or longer (the number used at recent conference) before any significant new safe, "directed" therapeutic approach is possible. If we start from "scratch" then that time course is certainly realistic. The "autistic" field is still scattered in many directions, unfortunately increasingly chasing ideas that will likely be dead ends, or "pieces" of the truth, but not attacking the "big picture." Why is that true? With the rapid acceptance that this has become an "epidemic," science says, ***you cannot have an epidemic of any type of developmental or congenital disorder,*** it is **IMPOSSIBLE**, it has become **Illogical**! Therefore, any researcher currently looking and submitting research projects based on "Autism – a developmental disorder" is not looking at what is really happening in a vast majority / ?? all the children being labeled "Autistic Spectrum Disorder." This no longer makes any sense.

There are additional huge implications from the statement, "this IS a disease" (NOT a developmental disorder, a congenitally "miswired" brain, etc.)

1. "Disease" means these children were born with normally functioning brains that became dysfunctional. That means they can be fixed, in theory they can work normally, again.
    1. You cannot "fix" / recover from a developmental disorder, you can from a disease.
        - i. This has profound implications in light of the work from leading institutions showing the brain is more pliable than we thought (implying late redevelopment is still possible) and the importance of early, correct laying down of pathways / tracts – as the brain evolves and develops.
        - ii. WE need to focus on the idea of "redeveloping" a child's brain, not "training" an "autistic" brain
        - iii. Parents are told there children can never fully "recover," - as a disease, we ***must expect*** recovery, hopefully be able to one day use the word "cure."
2. An educator or child development specialist looking at these children, must understand the concept of a "dysfunctional, but potentially normal brain" if they are truly going to be able to look at how to maximize each child's development.
    1. I have personally been appalled over the last few years at the lack of expertise in the "autistic" field available to truly help parents redevelop, re-educate their child's brain. I am sure these specialists exist, but in general they have not been in the circles accessible to parents at present, OR have not looked upon these children for what they really are.
        - i. To listen to an educational therapist who truly understands how to assess and work with the various "highs and lows" in how these children's brains are working, is impressive; much less a speech pathologist who understand the apraxia, and how to work with the oral motor dysfunction dominating these children (when you stop thinking of them as "autistic").
    2. Unlike the "old" ideas of NOT expecting speech development past ?? 5 or 6 years old, this means older children (10 – 14 years old / clinical experience to date) can be helped to redevelop speech.
        - i. When looked upon as a disease, this should be expected, not hoped for or discounted as "impossible."
3. Behaviorally, it has become apparent that one must treat these children age appropriate for where they are psychosocially, not chronologically, not as "retarded."
    1. With the realization that most of these children are truly intelligent . . .
        - i. Much of the negative behaviors seen, are because these children are not "disciplined" as one would discipline a normal 2, 4, 6 years old child (again where is the child psychosocially, not current "calendar" age) or are outright miserable, in pain, frustrated, angry, and NEVER looked at or truly understood in that way

One day we are all going to realize what a true tragedy this has become. How many / most of these children are "miserable" / physically suffering. If it's going to happen (and every scientific pathway is toward neuro-immune, an understanding of this as a disease) one day, why not NOW (before many more children are truly not recoverable). Unfortunately, "problems" continue to exist, which are working to slow down the rapidly needed change for all the children and families out there:

1. As illustrated above, every "assumption" made not based on good, solid medical science only serves to mobilize "academic" medicine against these efforts, instead of helping correctly focus on this crisis (and potential real solutions).
2. Many current efforts report "improvements" / "success"
    a. Unfortunately, many "remedies" can create some "success" IF graded in terms of their child starting off "autistic," metabolically dysfunctional, etc. – but these "success" stories in general do not come close to a real "normalization" of an "ill" child
        ii. Again, sights, expectations, measurements of "success" are changed dramatically if one recognizes the disease process going on here (scientific), not the old idea of a developmental disorder, developmentally mis-wired brain (now illogical, sci-fi).
3. Since this is not starting as a developmental or metabolic disorder (immune / viral are the **only** possible "causation" pathways scientifically), then treatment metabolically may help, but does not have the potential to truly fix this type of dysfunction
    a. IF thought of as a disease, then again, the bar of judging success (AND safety) changes dramatically
    b. You only beat, solve, potentially cure a disease by treating the etiology / causation, NOT the after effects
4. Parents are afraid:
    a. Yes, it has now come up in many discussions that one of the reasons for the failure to focus and mobilize quicker around the NIDS effort, is the fear of all the promised answers before, the false hopes of the past. I have had parents discuss the "pain" of having to "again" reevaluate a child's life, expectations, problems, "knowing" higher goals are possible / realistic, NOT impossible. but still so difficult to obtain.
        iii. Unlike any effort in the past, the NIDS effort is based on science, new information, new technologies
            1. While I can be pointed to merely as another "clinician," the NIDS medical board is composed of researchers who are leaders in their fields, who would never gamble their reputation or prestige on doing any study that was not based on hard, good, science and logic.
                a. As noted above, the NIDS hypothesis has been validated by every pharmaceutical company that has reviewed it to date.
            2. At this point in time, unfortunately, it is far more likely parents are one day going to be very upset for "believing" the current Autistic efforts, and at those groups / leaders for not "focusing" on neuro-immune faster, or recognizing its role / place, rather than those who have begun to follow a NIDS direction
                a. This is SCIENCE, this is becoming / will become reality

So how do we make this change?:

- Enough parents must focus around the NIDS effort that we can overcome, bypass the unfortunate "opposition" / negative momentum to change that exists presently
    - This is finally possible, but as noted above, will not happen without effort, help and support for the NIDS Medical Board.

- IF financial goals are met (a total business package of ~ $750,000 – see www.nids.net) there is a standing commitment for at least one (optimistically more) company with an immune modulator, to initiate trials for the children in a maximum of 6 – 8 months (from when the money is in place, and the network begins to come together)
    - This is an unheard of opportunity for all the children out there, but will not occur without successful implementation of the NIDS Business plan, and support for the NIDS Medical Research Board's efforts.
- We must all demand, insist that any significant allocation of funding, etc. be based on the "disease" state occurring, and focus funding on researchers beginning to look that direction, not still pursuing the old ideas of a developmental disorder

An unprecedented opportunity is possible as we enter the new millennium, IF we can "focus" upon a radically different, but now scientifically logical approach for the children, rather than continue to pursue old ideas, that no longer hold scientific logic. Changes can occur quickly. While I have said and written "patients, parents, have never before truly changed the course of medical therapy," that can be made to happen now. Through application of solid, good science, but via the connection (thanks to technology) of outstanding, leading researchers (not limited to one university set of connections), we enter the new millennium with a chance to truly radically, make this change happen, succeed now. As noted many times, the formation of the NIDS Medical Board was done to assure all of you by the level of researchers involved, that there will truly be a scientific level that will be appropriate, unchallengeable, but accelerated clinically in favor of your children.

What happens at this point is purely up to those of you able to read this (sadly, many organizations and groups continue to resist posting or presenting information, facts, that do not fit what they want their supporters, members to hear). There are NO medical or logistical obstacles (short of adequate funding and finding the appropriate research assistants, staffing, etc.) stopping this from occurring in the next 6 – 8 months, BUT if many parents remain unaware of this option, or continue to be told "it can't occur," when in reality (as presented at the NIDS conference Bethesda, June 1999) this can occur, it truly will not just happen (this is not how the "system" normally works). This STILL represents a major jump in academic focus and assumptions. It will not just happen by wishing or by itself (this is not the "natural" evolution of medicine), but with support, help, it CAN occur. With it will hopefully come the increased focus by new therapists with an understanding of rehabilitation in children, and a change in focus by existing therapists and the education system, such that we truly begin to understand how to maximize a child's development and potential, not hope to "train" a child with Autism (remember: you can't cure / fix a developmental disorder, but you can a "disease" state!) As another parent recently noted, *a child with "Autism" is not suppose to be able to recover, develop "functions" they are not suppose to have, rather one tries to compensate and work with the dysfunctions.* A child with a disease can be treated and expected to recover, especially if caught early enough, before the "disease" state can create permanent damage or injury.

In the past I had been told don't give false hope to parents. Perhaps, as has been expressed, it remains that fear (played upon by many old organizations), skepticism, that will keep this effort from achieving the support it needs. IF that happens, that will truly be a major crime (recognized 5 – 10 years from now). Again, focusing on SCIENCE, (not false promises, convoluted explanations or ideas), science now says this does make sense. There is reason for all of you to have hope, NOW, as we enter the new millennium.

So, with increased hope for the year 2000 – this can be made to happen ☺

Michael Goldberg

Michael Goldberg, MD

Addendum: Parents have asked what to do if "friends" or others wish to support the NIDS effort.

1. The NIDS Research Institute is fully "non-profit" / tax exempt. Donations can be made out to **"NIDS Medical Board & Research Institute"** and sent in care of my office or sent to NIDS c/o MAT @ P.O.Box 5938, Glen Allen, Virginia, 23058
2. Helping in any way to spread the awareness of this effort, the science of the NIDS hypothesis, the boards efforts, etc. will all help in overcoming the last barriers, the last obstacles to making this finally happen.

(Note: As has been discussed recently, this effort is meant to represent an enlarging collaboration of researchers around the world and is open to support and participation by any and all existing groups. The intent is to welcome any and all who want to help "focus" on this effort and make it succeed. There are meant to be no "old" politics or barriers in the way, it is time we all made a new start for these children.)

NEUROSPECT: ASSESSMENT OF ABNORMAL DISTRIBUTION OF RCBF IN CFIDS VS. "AUTISTIC SYNDROME CHILDREN."

Michael Goldberg, Ismael Mena, Bruce. Miller, and Carmen Thomas.
Dept. of Nuclear Medicine, Imaging Center, Harbor UCLA Medical Center, Torrance, Ca.

OBJECTIVE: To compare NeuroSpect finding in 25 children diagnosed "Autistic Syndrome / PDD" with 13 children with CFS / CFIDS vs. normals.

METHODS: We report on quantitative (Xe133) rCBF and high resolution HMPAO SPECT in 25 children meeting criteria of DSM IV for autism, compared with 13 children meeting CDC criteria for chronic fatigue syndrome (CFIDS) and 13 normal children (HMPAO). Ages were 5.5±2.5 years, 13±3 years and 9.3±3.2 years respectively. Male/female ratios were 22/3, 7/6 and 8/5 respectively. RCBF was imaged with a brain dedicated imaging device (Shimatzu, Headtome) after inhalation of 1.110 MBq of Xe133 gas, and with a high resolution fan beam collimator after IV injection of 370 - 740 MBq of Tc99m HMPAO. ROI's were determined manually for Xe133 and automatically set for HMPAO (64/ transaxial cut, in 6 adjacent 1 cm cuts above basal ganglia).

RESULTS:

	Xe133 rCBF (ml/min/100g)			
	Max. Flow	Min. Flow	Avg. Flow	
1. Autism	116±28 **	49±10 *	92±22 ***	lvs2
2. CFIDS	86±11	35±5	63±7	**lvs3
3. Normals			62±9x	

p<0.001 ***
0.002 **
0.02 *

x Chiron et al., J.Nuc. Med; 1992:33,696-703

In the Autistic children, maximal rCBF was observed in frontal lobes, while minimal rCBF was detected in temporal and occipital lobes and cerebellum. HMPAO uptake was 0.50±5 in occipital lobes and in frontal lobes 0.82±4, p<0.0001, while in Normals it was 0.78±5, without significant gradient. In the CFIDS children, **hypoperfusion is observed at 42 + 10 ml/min/100g, p < 0.0001 in the left temporal lobe and at 45 + 11, p < .001 in right temporal lobe. There is furthermore hypoperfusion with similar statistical significance in both parietal lobes and at 50 and 53 ml/min/100g, p < 0.05 in the frontal lobe of the right hemisphere.**

SUMMARY: **Brain Spect Scan results are presented along with some clinical observations of these particular groups of patients. This tool may open the door to a more physiologic/medical approach to this process in children. Comparisons are made with the finding in children with CFIDS and those "labeled" Autistic Syndrome / PDD. The observation of temporal hypoperfusion in adults and children with CFS/CFIDS, may help define Autism as a disorder of impaired relations with the surrounding environment determined by the temporal hypofunction leading as a consequence to a diaschetic hypofunction of visual cortex and cerebellum. The mechanisms for this abnormality need to be investigated using activation techniques and other approaches i.e.: evaluation of possible immune dysregulation, etc.**

ALASBIMN Journal

INDICE

FRONTAL AND TEMPORAL LOBE DYSFUNCTION IN AUTISM AND OTHER RELATED DISORDERS: ADHD AND OCD

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Cita/Reference:
Goldberg, M. Frontal and Temporal Lobe Dysfunction in autism and Other Related Disorders: ADHD and OCD. Alasbimn Journal1 (4): July 1999.
http://www.alasbimnjournal.cl/revistas/4/goldberg.htm

SUMMARY

Autism, Pervasive Development Disorder (PDD), Attention Deficit Hyperactive Disorder (ADHD), and Obsessive and Compulsive Disorder (OCD) involve significant frontal and temporal lobe dysfunction. This conclusion is based on NeuroSPECT work now in progress on children afflicted with these disorders. We have been using NeuroSPECT to image cerebral abnormalities of perfusion/function in Autism, ADHD, OCD, and other neuro-cognitive disorders.

With the increased focus and presentation of children labeled Autistic Syndrome / PDD, has come a greater need to understand and define the dysfunction in these children by objective "functional" quantification, now possible with new imaging technology such as NeuroSPECT.

The children have been evaluated by means of Xe133 for SPECT, expressing the results three-dimensionally and rCBF quantitatively in ml/min/100g; and qualitatively by means of Tc-99 HMPAO. The correlation of cerebral perfusion with brain function has been established, as NeuroSPECT is a useful tool for cerebral function assessment.

In this review paper, we will discuss our clinical observation and our rCBF findings for Autism and these related disorders.

The New Definition of Autism

Autism as classically defined was a severely incapacitating disability that was relatively rare. Its onset was in early childhood. This disorder was characterized by delays in language development, marked social deficits and a limited range of stereotyped repetitive behaviors. It occurred in approximately 1-2 out of every 10,000 births. Boys were afflicted more frequently than girls at a 3:1 ratio.

In this severe form of "Classic Autism" effective speech was absent. It could include symptoms of repetitive, highly unusual, aggressive and self-injurious behavior. Those afflicted had extremely abnormal ways of relating to people, objects, or events. Parents noticed that something was "not right" in the first three to six months of life.

Autistic infants did not demand attention, they did not enjoy being picked up, nor did they cuddle or cling when someone held them. They rarely smiled at other people or looked directly at them. In fact, they often appeared happiest when left alone. They resisted affection and did not interact normally. Mothers of autistic children often noted an understandable lessened pleasure in their maternal efforts. They complained that they felt they were caring for an "object" rather than a person.

In the last decade, another type of autism has surfaced that is often referred to as "Autistic Syndrome." Children suffering from this disorder appear **normal in the first 15-18 months of life.** They do not present signs or symptoms pediatricians or neurologists would find atypical. These children create an inconsistency with previous held beliefs that 70-80% of autistic children are mentally retarded. They crawl, sit up, walk, and usually hit normal motor milestones on schedule. Up until the age of onset, they are **affectionate** and appear to have above average **intelligence**.

Children with autistic syndrome may begin to develop some speech but then, without warning, they cease to progress, or begin to regress. Suddenly, these children become withdrawn. They are quiet sometimes and hyper at other times. Often self-stimulatory behaviors (i.e. arm flapping, rocking, spinning, or head banging) develop.

These children begin to display various abnormal behaviors in the preschool years often including:

- A need to preserve sameness
- Marked language abnormalities
- Indexes of developmental disorder - strange body movements, posturing and "soft" signs of neurological impairment

In time, some manifest symptoms that are both similar and atypical to children previously diagnosed as "classically autistic." What was once a relatively rare disorder is now twenty times more likely to occur.

In the past, autism was considered a "psychiatric" disorder. We now know that autism is a "medical condition," not a mental disorder. Perhaps one of the reasons no one has come up with an answer for autism is the way we have thought of it (or rather did not think of it in medicine).

Most researchers did not look for the answers to autism because they felt this was a disorder that was untreatable medically. Treatment for this affliction was primarily left in the hands of psychologists and a few psychiatrists.

Even though children with classic autism might be helped medically as our knowledge of the brain's physiology expands, for now it might be helpful to separate children afflicted with autistic syndrome from those with classic autism. As children with autistic syndrome increasingly become categorized as a "medical" problem, separating them from the many negative connotations and hopelessness associated with "classic" autism could be advantageous to promoting research and funding to help these children. The differences between the two groups may be summarized as follows:

Classic Autism

- A rare disorder affecting 1-2 children / 10,000
- Some/many individuals may have early signs of neurologic injury
- Some may have "physiologic/immune" factors / variables, "treatable" medically by current and future immune medicines
- Generally "abnormal" early (i.e. 3 - 6 months of age)
- "Classic" Autistic symptoms / presentation
- Presumed "static" / unchangeable

Autistic Syndrome

- An increasing population of children with "Autistic/ PDD" behavioral characteristics.
  - Atypical symptoms
  - Asperger's
  - Landau Kleffner's
  - ADHD / ADD variant
- Current estimate 20-40 children / 10,000 (incidence may be as high as 1-5%)
- Does NOT have "objective" physical signs of neurologic damage
- Majority (possibly all) are immune mediated, appropriately looked upon as a medical dysfunction - open to potential medical therapy
- Generally "normal" early (usually until 15 - 18 months of age)
- Potentially progressive disorder (if not treated / corrected) which may explain the origin of many cases of Landau-Kleffner syndrome

Etiology

While the cause of autism is speculative, different theories that have surfaced in the past include:

- Brain injury
- Constitutional vulnerability
- Developmental aphasia
- Deficits in the reticular activating system
- An unfortunate interplay between psychogenic and neurodevelopmental factors
- Structural cerebellar changes

With the relatively new thinking that autism has medical origins have come several other theories. Some doctors believe autism is a result of a metabolic, enzyme, or genetic defect. Although a few children may suffer a built-in genetic or functional defect present since early gestation, our clinical observation and our rCBF findings for Autism do not support these theories for the majority of children afflicted. These theories do not fit or began to explain the large increase in the number of children diagnosed with autism today.

RESEARCH TO SUPPORT IMMUNE DYSFUNCTION THEORY

Similarities between behavioral deficits reported in animals with hippocampal lesions and autistic behavior have been noted by Boucher and Warrington (1). They found memory deficits in infantile autism similar to the memory deficits found in the amnestic syndrome. Medial temporal lobe damage on pneumoencephalograms has previously been reported in a subset of autistic children (2). These findings were particularly evident on the left side. Damasio and Mauer have also proposed that "the syndrome results from dysfunction in a system of bilateral neural structures that includes the ring of mesolimbic cortex located in the mesial frontal and temporal lobes, the neostriatum, and the anterior and medial nuclear groups of the thalamus." (Noteworthy, is that much emphasis is put on the medial temporal lobe).

By definition, autism has an early onset before 30 months of age, while disorders appearing later in life have been thought to be symptomatically different from autistic handicap conditions. Publications over the last 13 years have cast some doubt on these relationships. It has been pointed out that there is no firm evidence that similar or identical syndromes might not develop in older children (3).

Autism can be associated with a variety of disorders affecting the central nervous system including encephalitis. In 1981, DeLong, Bean, and Brown described three children between 5 and 11 years of age who developed autistic features while having an encephalitic illness. One patient had high serum herpes simplex titers, and a CT scan revealing a lesion of the temporal lobes, mainly on the left side. The other two patients had normal CT scans.

Gillberg in 1986 described the case of a 14-year old girl who developed a "typical" autistic syndrome after an attack of herpes simplex encephalitis (4). Widespread bilateral destruction of the brain parenchyma and the temporal lobes was found on CT; there was also some involvement of the lower parts of the parietal lobes. The autistic symptoms persisted long after the acute phase of the encephalitic illness.

In 1975 an article was published in Cortex (5) describing a syndrome similar to autism in adult psychiatry, involving loss of emotional significance of objects, inability to adopt in social relationships, loss of recognition of the significance of persons, and absence of sustained purposeful activity after temporal lobe damage.

In 1989 an article appeared in the Journal of Autism and Developmental Disorders (6), describing a 14-year old boy, with a normal history until the second grade, when he was admitted to the hospital with herpes simplex encephalitis. Later he developed significant language, social, and memory deficits. The research group commented on the cognitive and behavioral deficits caused by temporal lobe damage in herpes encephalitis. While other studies have also implicated the temporal lobes in the pathogenesis of autism (7)(8) this does not prove a common association between temporal lobe pathology and autism. Research has found a variety of lesions in the brain, particularly the cerebellum (9) since Herpes virus has a predilection for the temporal lobes (10) it is possible to hypothesize that there is an association between temporal lobes and autism, but not necessarily a direct cause and effect relationship (11). It is equally important to note that failure of development in temporal lobes early in life may produce different symptoms from those arising out of a later destruction of previously normal lobes.

From the Journal of Clinical Immunology and Immunopathology, Singh et al. hypothesized that autoimmunity secondary to a virus infection may best explain autism in some children (12). Congenital rubella virus (13) and congenital cytomegalovirus (14) have been indirectly involved as causative factors in autism. Researchers found evidence for autoimmunity as a possible mechanism to explain autism, based on a cellular immune response to myelin basic protein (15), antibodies against putative brain serotonin receptors(16), and neuron-axon filament proteins of the nerve cell. (17)

Autism and the Immune System

It is our belief that "Autistic Syndrome" probably is a state of dysfunction induced in the brain by a dysregulated immune system. It is possible that this dysfunction may occur in individuals that have a genetic predisposition. In theory, this predisposition could be triggered by various stresses placed on the child's immune system. It's severity varies with the individual and age of onset.

It can be compared to blindness. There are many people who are blind, but the cause of their blindness may be very different. For whatever the reasons (genetic, environmental, a combination of viruses, etc.), what is occurring appears to be an immune mediated, abnormal "shut down" of blood flow in the brain and therefore central nervous system function.

In adolescents and adults, this dysfunction may manifest itself as CFIDS (Chronic Fatigue Immune Dysfunction Syndrome), ADHD, and various other atypical auto-immune disorders associated with neuro-immune dysfunction. In older children, it is seen as variants of ADD (Attention Deficit Disorder) / ADHD. And in younger children/infants, it appears as autism, autistic syndrome and PDD (Pervasive Development Disorder).

The multiple metabolic, physiologic, and immune markers that are abnormal in these children, "make sense" when you think of the bigger picture and consider the primary cause of autism as immune dysfunction, creating multiple cellular / mitochondrial dysfunctions.

This offers an explanation for the progressive process of the autistic syndrome that occurs sometime between 15-24 months of age. It is this immune mediated, abnormal "shut down" of blood flow in the brain that affect the language and social skills area of the brain and central nervous system function.

Clinical Manifestations

Typical characteristics include:

- nondeveloped or poorly developed verbal and nonverbal communication skills
- abnormalities in speech patterns
- impaired ability to sustain a conversation
- abnormal social play

- lack of empathy
- an inability to make friends

Also frequent seen are:

- stereotypic body movements
- a marked need for sameness
- very narrow interests
- preoccupation with parts of the body
- change of hand or becomes ambidextrous, as they turn autistic.

With several different etiologies or biological causes, autism is considered a syndrome rather than a disease. Some researchers have proposed genetic defects (18),viruses (19)(20) and immunological ties(21)(22)(23) to be the cause.

While the literature has speculated regarding the above hypothesis and many others, at this time there appears to be an enlarging group of children, whose origin seems linked to the concept of an Immune-Dysregulatory phenomenon. The dysfunction / lack of blood flow can eventually lead to injury of nerve cells, which offers a possible explanation for the abnormal brain waves and the large numbers of autistic syndrome children suddenly being labeled as "Landau-Kleffner."

Whether due to an underlying viral, retro-viral, or other related entity, a likely underlying genetic disposition, and/or other "environmental"factors, the number of children affected seems to be rapidly increasing. Many of these children do not fit classic autistic profiles, but are frequently labeled high functioning autistic, atypical autistic, PDD, etc.

NeuroSPECT Results

Quantitative rCBF measurements with Xenon 133 were found to be significantly higher than normal in autistic children, with maximal values in the frontal lobes and visual cortex. Minimal perfusion was observed in the temporal lobes. Decreased flow was also noted in the cerebellum and occipital lobes.

The areas of increased perfusion, most frequently located in lateral frontal lobes, are similar to our observations in obsessive compulsive disorder (OCD children). Tc 99m HMPAO images (Prado et al.) demonstrate increased frontal perfusion, and demonstrating also temporal, occipital and cerebellar hypoperfusion. Figure 1.

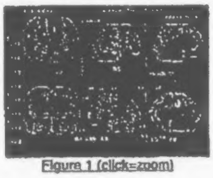

Figure 1 (click=zoom)

In children with OCD there is a significant increase in frontal perfusion observed bilaterally in a large number (~ 81%) of the children and unilaterally in a limited number (6%) of the children, with a total of 87% of children demonstrating increased frontal perfusion. Among 50% of these children there is also increased perfusion in the posterior cingulate gyrus. Of note, there is furthermore hypoperfusion of temporal lobes mostly in the mesial aspects in 93% of OCD children examined to date.(Mena et al)

Increased frontal perfusion was also reported (Rubin et al.) in adults. Most probably this phenomenon denotes a co-morbidity phenomenon also that is clinically observed between autism and obsessive compulsive disorder.

Discussion of NeuroSPECT Results

NeuroSPECT scans are becoming extremely informative, as they show blood flow through areas of the brain. Blood flow implies function / activity (24)(25). As noted, the autistic children have presented consistently with a decrease in blood flow in the temporal area, various degrees of hypoperfusion in the parietal / occipital area and the cerebellum vermis. There has often been an increase of blood flow in the frontal lobes which is consistent with ADD on the hyperactivity end. Figure 2.

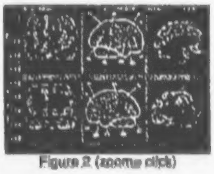

Figure 2 (zoom= click)

The clinical implications of these findings has been heightened by the fact that the "anatomic" areas of the brain involved on the NeuroSPECT have correlated with predicted areas of dysfunction when reviewed by neuro-anatomists (research work in progress). In fact, the areas of dysfunction on Neuro-SPECT, have helped explain readily the physiologic dysfunction of these children.

These children present with a symptomatology consisting primarily of severe speech and language development (Left temporal lobe) and severe social difficulties (Right temporal lobe), often some fine, not usually gross, motor difficulties (cerebellar involvement), and various learning difficulties and attention deficit dysfunctions consistent with involvement of frontal and temporal lobes, and links to areas of parietal-occipital dysfunction. They may also have many symptoms consistent with OCD characteristics, associated with these areas of dysfunction.

In 1995, Mountz, Tolbert, Lill, Katholi and Liu reported their HMPAO findings in 6 children with severe autism and demonstrated with semi-quantitative techniques temporal and parietal hypoperfusion with lateralization to the left hemisphere, while in two of the three images published there is a maximal perfusion in the lateral frontal lobes.

Georges, Costa, Coniz, Ring and Ell reported in four autistic adults with Tc-99 HMPAO diminished rCBF in temporal and frontal lobes. The temporal abnormality appears to be confirmed mostly in adults, adolescents, and children suffering of autism. Thus, damage to temporal lobe in an early developmental stage may result in autistic manifestations.

The results are otherwise heterogeneous translating the heterogeneity of the autistic population, denoting the presence of occipital hypoperfusion and cerebellar hypoperfusion mostly in the mesial aspects corresponding to the vermis area. This later observation correlates with reports in the literature of atrophy of the cerebellar vermis demonstrated by MRI technique. Further heterogeneity in our group of patients is

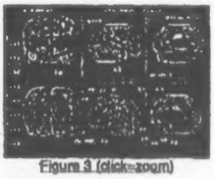

Figure 3 (click=zoom)

demonstrated by apparent comorbidity with OCD (and ADHD) in these children and their typical presentation of increased perfusion in lateral frontal lobes. (Figure 3)

Conclusions and Discussion:

Autistic children are an heterogeneous group. Increased frontal perfusion may be related to "hyperfrontality" disorder, and cerebellar hypoperfusion to motility impairment. Temporal lobe hypoperfusion and other areas of dysfunction remains in spite of multiple various therapies used by these children. We are looking at anatomical markings, defining autism / PDD dysfunction, correlating to models proposed by behavioral neurologists.

Past focus for autistic children has been on trainability, cooperation, behavior, NOT on improving the cognitive processing. A shift to the idea of "rehabilitation" is already in motion, a full review of techniques and goals is urgently needed.

Based on NeuroSPECT findings, implications are that medications or efforts to "calm" the brain and child down, may further shut down the areas in which we want to improve blood flow and function and down regulated blood flow.

Clinical experience to date has noted with medical intervention to help normalize their dysregulated immune systems many of these children up to 5 or 6 years of age will often "turn-on" and pick-up where they stopped, generally about 18 - 24 months old. On the other hand, as children approximately 6 - 10 or 11 years improvement is a slower process, often requiring more "help" to "learn" the basics, grow-up developmentally, and then move ahead successfully.

For most children, it will probably take the advent and usage of new drugs that are immune modulators, to truly shut off their dysregulated immune system. Although these drugs are already in existence and are now undergoing new usage testing in adults, they still await testing for children. Hopefully, they will have the ability to adjust the dysregulated function and put the immune system back on track. The clinical implications and concepts related to past hypotheses of brain develop and maturity, are intriguing to say the least.

It was and still is believed by noted neurologists that nothing can be done medically to treat these children. Fortunately, as these children are changing with therapy, respected neurologists and other pediatric researchers, are beginning to feel it is time to "take a second look."

The good news is that children afflicted with autism whose immune systems have been helped are showing they are bright thinking individuals who are not what the world expected. Children with the "label" of Autism / PDD usually are not retarded. They may have normal or above normal intelligence. They are not throw away kids that cannot be helped. They are children who are suffering from temporal hypoperfusion / hypofunction, likely auto-immune mediated dysfunction, that can possibly recover.

While identifying and looking at different neurotransmitters, neuroscientists have also found different problems with too much or too little of one or the other. In people with too much norepinephrine everything is pumped up; every stimulation demands a response. The other side of the coin is that a shortage of norepinephrine seems to rob people of the ability to know what's important. Working memory (the part that stores information while the mind considers if it is worth keeping and where to file it) fails without enough dopamine. Altered central dopaminergic function in the midbrain has been implicated in the pathogenesis of Tourette's Syndrome. Finally, shortage of serotonin in the frontal lobes and in the brain's limbic system seems to relate to impulsivity; obsessive-compulsive symptoms may be caused by a serotonergic defect involving the basal ganglia.

Summary:

The observation of temporal hypoperfusion in adults and children with CFS / CFIDS, may define autism as a disorder of impaired relations with the surrounding environment determined by the temporal hypofunction leading as a consequence to a diaschetic hypofunction of visual cortex and cerebellum. The mechanisms for this abnormality need to be investigated using activation techniques and other approaches i.e. evaluation of possible immune dysregulation, etc.

With the general finding of a physiologic hypoperfusion / hypofunction on NeuroSPECT, with generally normal MRI's and CAT scans, we are optimistically looking at areas of dysfunction amenable to therapy and improved return of function. Work is beginning (clinical research in progress) to define reasons for this function and in turn potential avenues of therapeutic intervention.

REFERENCES

1. Boucher J, Warrington, "EK: Memory Deficits in Early Infantile Autism: Some Similarities to the Amnesic Syndrome," *BR J Psychol* 1976;67:76-87

2. Hauser SL, DeLong GR, "Rosman NP: Pneumographic Findings in the Infantile Autism Syndrome: A Correlation with Temporal Lobe Disease" *Brain* 1975, 98:667-688

3. Waterhouse, L., Fein, D., Nath, J., & Snyder, D. (1984), "Pervasive Schizophrenia Occurring in Childhood: A Review of Critical Commentary." *In American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders(DSM-III):* An interim appraisal. Washington, D.C.

4.Gillberg, C.(1986), "Brief Report: Onset at Age 14 of a Typical Autistic Syndrome. A Case Report of a Girl with Herpes Simplex Encephalitis," *Journal of Autism and Developmental Disorders*, 16,369-375

5. Marlowe,W. B., Namcall, E.L., & Thomas, J.J. (1975), "Complete Kl¸Ver-Bucy Syndrome in Man," *Cortex* 11, 53-59

6. Greer,M K, Lyons-Crews, M., Mauldin, L.B. & Brown, F. R. III. (1989), "A Case Study of the Cognitive and Behavioral Deficits of Temporal Lobe Damage in Herpes Simplex Encephalitis," *Journal of Autism and Developmental Disorders* 19, 317-326

7. Hetzler, B., & Griffin, J.(1981), "Infantile Autism and the Temporal Lobe of the Brain," *Journal of Autism and Developmental Disorders* 11, 317-330

8. Jones, P.B., & Kerwin, R.W. (1990), "Left Temporal Lobe Damage in Asperger's Syndrome," *British Journal of Psychiatry* 156, 570-572

9. Courchesne, E. (1991), "Neuroanatomic Imaging in Autism," *Pediatrics* 87(Suppl.part 2), 781-890

10. Greer,M K, Lyons-Crews, M., Mauldin, L.B. & Brown, F. R. III. (1989), "A Case Study of the Cognitive and Behavioral Deficits of Temporal Lobe Damage in Herpes Simplex Encephalitis," *Journal of Autism and Developmental Disorders* 19, 317-326

11. Ghaziuddin, M. Tsai, L.Y., Eilers, L. & Ghaziuddin N. "Brief Report: Autism anD Herpes Simplex Encephalitis," *Journal of Autism and Developmental Disorders* Vol. 22, No. 1,1992

12. Singh V.K. , Warren R.P. Odell J.D. , and Cole P., "Changes of Soluble Interleukin - 2, Interleukin - 2 Receptor, T8 Antigen, and Interleukin - 1 in the Serum of Autistic Children," *Clinical Immunology and Immunopathology* 61, 448-455 (1991)

13. Chess, S., "Autism in Children with Congenital Rubella," *J. Autism Childhood Schizophrenia* 1, 33-47, 1971

14. Stubbs, E.G., Ash, E. and Williams, P.S., "Autism and Congenital Cytomegalovirus," *J. Autism Dev. Disord.* 14, 249-253, 1983

15. Weizman, A. , Weizman, R., Szekely, G.A., Wijsenbeek, H., and Livni, E., "Abnormal Immune Response to Brain Tissue Antigen in the Syndrome of Autism," *Am. J. Psychiatry* 7, 1462-1465, 1982

16. Todd, R. D., and Ciaranello, R. d., "Demonstration of Inter- and Intraspecies Differences in Serotonin Binding Sites by Antibodies from an Autistic Child," *Proc. Natl. Acad. Sci. USA* 82, 612-616,1985

17. Singh, V.K., Fudenberg, H. H., Emerson, D. and Coleman, M., "Immunodiagnosis and Immunotherapy in Autistic Children," *Ann. N. Y. Acad. Sci.* 540, 602-604, 1988

18. Folstein, S. & Rutter, M. (1977), "Genetic Influences and Infantile Autism," *Nature*, 265:726-728

19. Chess, S.(1977),"Follow-up Report on Autism in Congenital Rubella," *J. Autism Dev. Disord.*,7:69-81

20. Stubbs, E.G. (1978), "Autistic Symptom in a Child with Congenital Cytomegalovirus Infection," *Journal of Autism- and Childhood Schizophrenia, 8:37-43*

21. Stubbs, E.G. (1976), "Autistic Children Exhibit Undetectable Hemagglutination-Inhibition Antibody Titers Despite Previous Rubella Vaccination," *Journal of Autism and Childhood Schizophrenia*, 6:269-274

22. Stubbs, E.G.,Crawford, M. I., Burger, D.R. % Vanderbark, A.A. (1977). "Depressed Lymphocyte Responsiveness in Autistic Children," *Journal of Autism and Childhood Schizophrenia*, 7:49-55

23. Warren, R. P., Stembridge, A. M. & Gardner, E.J. (1985), "Deficient Immune Function of Peripheral Blood Mononuclear Cells from Patients with Gardner Syndrome," *Clin Exp. Immunol.*, 60:525-531

24. Ichise M, Salit IE, Abbey SE, Chung D-G, Gray B, Kirsh JC, Freedman M. "Assessment of Regional Cerebral Perfusion in 99 Tcm-HMPAO SPECT in Chronic Fatigue Syndrome," *Nucl Med Comm* 1992; 13: 767-772

25. Costa DC, Brostoff J. Ell PJ. "Brain Stem Hypoperfusion in Patients with Myalgic Encephalomyelitis- Chronic Fatigue Syndrome (abstr.)" *Eur J Nucl Med* 1992: 19(8): 733

26. Prado C.. and Mena I.. Basal and frontal activation neuroSPECT demonstrates functional brain changes in major depression. Alasbimn Journal1(3): April 1999.
http://www.alasbimnjournal.cl/revistas/3/pradoia.htm

27. Mena I., Solo,C.,Neubauer, S.,de la Barra,F., Garcia,R., Prado,C., Obsessive compulsive disorder in children: Spet of 99mTC HMPAO findings. World Congress of Nuclear Medicine, Berlin, 1998. European Journal of Nuclear Medicine 25:1077,1998

Summary | Introduction | Research to support inmune dysfunction theory | NeuroSPECT Results | Discussion | References | Complete version | Article home

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PEDIATRICS & YOUNG ADULTS
ADHD/ADD - LEARNING DISABILITIES
IMMUNE DYSFUNCTION
AUTISM

Autism and the Immune Connection

Infantile autism begins early in life, usually before the child is 30 months of age. While "in the past" a rare condition with a "disputed" incidence of just 2-5 in 10,000 live births, it is seen as a devastating handicap on psychologic and neurologic development, with potentially long-term serious consequences. As described in the past, Autistic infants did not demand attention, they did not enjoy being picked up, nor did they cuddle or cling when someone held them. They rarely smile at other people or look directly at them. In fact they often appear to be the happiest when they are left alone. Mothers of autistic children have noted an understandable lessened pleasure in their maternal efforts. They complain that they feel they are caring for an "object" rather than a person. Sometimes this condition is not noticed at first, because physical development generally appears normal in the autistic infant. These infants are often viewed as "placid" babies.

These children begin to display various abnormal behaviors in the preschool years often including:

1. A need to preserve sameness
2. Marked language abnormalities
3. Indexes of developmental disorder - strange body movements, posturing and "soft" signs of neurological impairment

Etiology

While the cause of autism is speculative different theories have surfaced in the past including:

a) Brain injury
b) Constitutional vulnerability
c) Developmental aphasia
d) Deficits in the reticular activating system
e) An unfortunate interplay between psychogenic and neurodevelopmental factors
f) Structural cerebellar changes

With several different etiologies or biological cause's, autism is considered a syndrome rather than a disease. Some researchers have proposed genetic causes,[1] viral causes,[2,3] and immunological ties[4,5,6] to be the cause. An increased incidence of two or more miscarriages and infertility,[7] as well as preeclampsia[8] and bleeding during pregnancy,[9] have been shown to occur in mothers of autistic children. Perhaps the disorders occurring in pregnancy are affecting the fetus and showing up as autism in the children. Studies have also been done comparing the maternal antibodies of mothers with their autistic children.[10] These findings suggest that abnormal maternal immunity may be associated with autism because plasma reactivity against lymphocytes was found in several of the mothers. Antibodies reactive with lymphocytes of the father were also found, suggesting the target antigen of the reactivity was a parental antigen inherited from the father. Assuming maternal antibodies may be associated with the development of autism, McConnachie and McIntyre suggested maternal antibodies of mothers with repeated pregnancy losses caused fetal demise, causing immunopathy by reacting with antigens expressed on the trophoblast or extraembryonic tissues of the developing embryo.[11] It has been shown by some researchers that antigens on the trophoblast cross-react with antigens found on lymphocytes.[12,13] Conceivably, maternal antibodies could react with trophoblastic tissue, causing a transitory obstruction of blood flow to the fetus resulting in nonlethal brain damage. Equally, the abnormal behavior seen in autism might be caused by the immunopathological damage done to the developing neural tissue of the fetus by the maternal antibodies.

While the literature has speculated regarding the above hypothesis and many others, at this time there appears to be an enlarging group of children, whose origin seems linked to the concept of an Immune-Dysregulatory phenomenon. Whether due to an underlying viral, retro-viral, other related entity, a likely underlying genetic disposition, and/or other "environmental" changes, the number of children affected seems to be rapidly increasing. Many of these children do not fit classic autistic profiles, but are frequently labeled high functioning autistic, atypical autistic, PDD, etc.

PATHOPHYSIOLOGY:

Similarities between behavioral deficits reported in animals with hippocampal lesions and autistic behavior have been noted by Boucher and Warrington.[14] They found memory deficits in infantile autism similar to the memory deficits found in the amnestic syndrome. Medial temporal lobe damage on pneumoencephalograms has previously been reported in a subset of autistic children.[15] These findings were particularly evident on the left side. Damasio and Mauer have also proposed that "the syndrome results from dysfunction in a system of bilateral neural structures that includes the ring of mesolimbic cortex located in the mesial frontal and temporal lobes, the neostriatum, and the anterior and medial nuclear groups of the thalamus." (Noteworthy is that much *emphasis* is put on the *medial temporal lobe).*

By definition, autism has an early onset before 30 months of age, while disorders appearing later in life have been thought to be symptomatically different from autistic handicap conditions. Publications over the last 13 years have cast some doubt on these relationships. While the rationale for an age limit for the onset of autism has been discussed, it has been pointed out that there is no firm evidence that similar or identical syndromes might not develop in older children.[16]

Autism can be associated with a variety of disorders affecting the central nervous system including encephalitis. In 1981, DeLong, Bean, and Brown described three children between 5 and 11 years of age who developed autistic features while having an encephalitic illness. While these autistic features resolved after clinical recovery, one patient had high serum herpes simplex titers, and a CT scan revealing a lesion of the temporal lobes, mainly on the left side. The other two patients had normal CT scans.

Gillberg in 1986 described the case of a 14-year old girl who developed a "typical" autistic syndrome after an attack of herpes simplex encephalitis.[17] Widespread bilateral destruction of the brain parenchyma and the temporal lobes was found on CT; there was also some involvement of the lower parts of the parietal lobes. The autistic symptoms persisted long after the acute phase of the encephalitic illness. This case contributes circumstantial evidence that a full blown autistic syndrome may be produced by temporal (and parietal lobe) damage. (This author would note that this is consistent with the areas of decreased function being seen on NeuroSPECT scans with Dr. Ismael Mena - clinical research in progress.) It also furthers the evidence that herpes simplex encephalitis can cause an autistic syndrome. In 1975 an article was published in Cortex[18] describing a syndrome similar to autism in adult psychiatry, involving loss of emotional significance of objects, inability to adopt in social relationships, loss of recognition of the significance of persons, and absence of sustained purposeful activity after *temporal* lobe damage.

In 1989 an article appeared in the Journal of Autism and Developmental Disorders,[19] describing a 14-year old boy, with a normal history until the second grade, when he was admitted to the hospital with herpes simplex encephalitis. Later he developed significant language, social, and memory deficits. The research group commented on the cognitive and behavioral deficits caused by temporal lobe damage in herpes encephalitis. While other studies have also implicated the temporal lobes in the pathogenesis of autism[20,21] this does not prove a common association between temporal lobe pathology and autism.

Research has found a variety of lesions in the brain, particularly the cerebellum.[22] Confusion and differences may be due to the heterogeneity (differences) in possible etiologies or time/duration effects within this varied syndrome we label "autistic". However, since Herpes virus has a predilection for the temporal lobes,[23] it is possible to hypothesize that there is an association between temporal lobes and autism, but not necessarily a direct cause and effect relationship.[24] It is equally important to note that failure of development in temporal lobes early in life may produce different symptoms from those arising out of a later destruction of previously normal lobes.

NeuroSPECT scans are becoming extremely informative, as they show blood flow through areas of the brain. Blood flow implies function/activity.[25,26] As noted, the Autistic children that I have been able to obtain NeuroSPECT scans on (limited by age and affordability), have shown a decrease in blood flow in the temporal (and parietal) areas. Consistent with the reports of temporal lobe dysfunction in Autistic kids, this is a very logical finding. Surprisingly, and without good explanation, is the finding of increased blood flow in the frontal lobes which is consistent with ADD on the hyperactivity end. (Note: While this may explain occasional success in the usage of Ritalin with some Autistic children, Ritalin has the effect of decreasing blood flow on the whole brain. Therefore, while helping the child if there is too much flow in the frontal area, you may not be helping "over all" if you are cutting flow in areas that are already low, such as in the temporal or parietal areas).

It is also interesting to note that in my working with Chronic Fatigue Syndrome, "Immune Dysregulation" for the past 12 years, in a recent study (pending publication) we have observed a significant diminution of blood flow in children suffering from CFS/CFIDS in both temporal and, to a lesser degree, the parietal lobes. It is this researcher's opinion that there is a strong connection between various immune dysfunctional/dysregulatory states appearing over the last 12 - 13 years and the emergence of an onslaught of "atypical" autism.

From the Journal of Clinical Immunology and Immunopathology, Singh et al. hypothesized that autoimmunity secondary to a virus infection may best explain autism in some children.[27] Congenital rubella virus[28] and congenital cytomegalovirus[29] have been indirectly involved as causative factors in autism. Researchers found evidence for autoimmunity as a possible mechanism to explain autism, based on a cellular immune response to myelin basic protein,[30] antibodies against putative brain serotonin receptors,[31] and neuron-axon filament proteins of the nerve cell.[32] About 67% of the autistic sera contained antibodies to NAFP. They were present in almost all patients with abnormal cell-mediated immunity(CMI). An interesting observation was that the sera from household contacts was also positive for anti-NAFP (46% of the siblings or 55% of the parents). Antibodies to NAFP have been previously reported in neurotropic "slow virus" diseases (Kuru and Creutzfeld-Jacob disease) in man.[33] Other studies of household contacts of patients with degenerative disorders of the brain have revealed anti-NAFP to be highly prevalent,[34,35] suggesting an association of an infectious agent (i.e. slow virus) in the etiology of these diseases. With this hypothesis, eight patients (six with abnormal CMI and two without the defect) were placed on immunomodulant therapy. In six patients, parameters in T-cell function and defects in AMLR were partially corrected. Improvement was noted in terms of clinical status, speech, sleep, and attention. After 8 weeks they could speak more than one command; after 16 weeks they were able to write a complete sentence; and all had increased attention span and or ability to sleep. The two patients without abnormal CMI were nonresponders.

This research has also shown a significant depression of CD4+ T helper cells and their suppresser- inducer subset,[36,37] with an increased frequency of the null allele at the complement C4B locus[38] in children with autism. As similar changes have been known to occur in other autoimmune diseases,[39,40] these researchers postulate that the increase of serum concentrations of sIL-2 (soluble interleukin 2) and sT8 antigens indicates immune activation of a T-cell subpopulation that may be important in the etiology of the disorder in some children with autism. In a fashion similarly proposed for Alzheimer's disease,[41] it is possible that an anatomical alteration in the brain, particularly the hypothalamus (because of its role in controlling emotions and behaviors) of autistic children, may result in a functional disturbance of the neuroendocrine-immune axis. Further investigation is necessary. Many of the Autistic children I have been evaluating have shown very high T-4 and T-8 counts.

While reactions to MMR (measles/mumps/rubella) vaccine are in general mild,[42] cases of meningoencephalitis occurring in the third and fourth week post-vaccination have been reported in the UK and elsewhere.[43,44,45,46,47] Starting in February of 1990 the British Paediatric Surveillance Unit asked all paediatricians to report all cases with one or more reactions occurring within six weeks of MMR vaccination. Reactions they were asked to look for included neck stiffness (or sign of meningism), extreme irritability, convulsions, altered consciousness, unexplained screaming attacks, motor or sensory deficit, visual disturbance, visual deficit or speech disturbance. In some of these cases mumps virus was cultured from cerebrospinal fluid (CSF) .

Nucleotide sequencing of virus isolates has enabled strains of vaccine origin to be separated from wild strains.[48] Definite cases of a vaccine-like strain of mumps virus were cultured from CSF.[49] While there was no sex differences in the cases reported overall, an excess of males (2:1) were reported in the definite or probable categories. Even though mumps occurs equally in both sexes,[50] complications of meningoencephalitis following both mumps vaccination or wild infection has been reported more frequently among males than females,[51,52] with ratios ranging from 3:1 to 5:1. One must bear in mind that the natural occurrence of meningoencephalitis following mumps infection is estimated to be 1 in 400 cases.[53] Before the MMR vaccine was introduced in the UK, mumps was responsible for a fifth of all reported cases of viral meningitis.[54] Mumps vaccine related meningoencephalitis is generally short lived or mild[55], but some permanent sensorineural deafness has been reported.[56] Published evidence indicates that vaccine reactions are rare and unlike the natural disease, does not lead to permanent sequel.

In this author's opinion, while the UK and Canada have focused on the MMR vaccine, both its mumps component and Rubella, there is much skepticism regarding the "true" incidence of mumps meningoencephalitis as reported above, and vaccine risk remains very doubtful, if existent at all. This country has not experienced or reported any significant problems with the MMR vaccine. While there may be a possible "triggering" factor with Rubella and an immune active state, this remains an unlikely cause of Autism. Unless further research creates a stronger connection, it remains safer to vaccinate a child than not. Consistent with the question of whether there is a peculiar or unusual immune reactivity when a child is younger, waiting till a child is 3 or 4 could not be faulted, but with ongoing measles outbreaks occurring at times, it is not something easy to recommend routinely at this time.

Another difficult position to address, is the possible role of fungi in the pathophysiology of Autistic dysfunction. Candida albicans is arguably the single most important fungal pathogen. Because it is a commensal organism present in virtually all human beings from birth, it is ideally positioned to take immediate advantage of any weakness or debility in the host, and probably has few equals in the variety and severity of the infections for which it is responsible.[57] Clinically, there is abundant inferential evidence that both mucocutaneous and systemic candidiasis are typically associated with defects or weaknesses in the cell-mediated immune response.[58] They may reflect specific deficiencies in this context, such as in chronic vaginal candidiasis[59,60] or chronic mucocutaneous candidiasis.[61] (One must note, that while one might anticipate neuro-cognitive dysfunction in these states, it is not a primary focus of discussion. Significantly, these states do not account for or induce an "Autistic" state of CNS dysfunction, seeming to negate many metabolic theories that abnormal metabolic products, seen in exceptionally high volume in these type of patients, induce Autism.)

Epidemiological studies of C. albicans have been hampered by the lack of precise and reproducible methods for identifying isolates. Whatever the ultimate role and pathogenesis of Candida, there seems to be no doubt that it can play a role in many pathologic conditions. Yeast is certainly a potential pathogen in any immune dysfunction/dysregulated state. Yeast may be seen as a secondary phenomenon due to a generalized immune dysfunctional state. A yeast "overgrowth" in the GI tract can interfere with nutrient absorption, altering Amino Acid and protein metabolism and thereby altering multiple body functions. I do believe that it is logical, if you are in an immune dysregulatory state, you may get an overgrowth in the G.I. tract. It is likely Candida may play a role in what is referred to as the "leaky-gut" phenomena. Some physicians believe you actually have a toxin released by the yeast and absorbed into the body, affecting the nervous system.

Clinical Manifestations

Typical characteristics include:
a) nondeveloped or poorly developed verbal and nonverbal communication skills
b) abnormalities in speech patterns
c) impaired ability to sustain a conversation
d) abnormal social play
e) lack of empathy
f) an inability to make friends

Also frequent seen are:
g) stereotypic body movements
h) a marked need for sameness
I) very narrow interests
j) preoccupation with parts of the body
k) changes handness or becomes ambidextrous, as they turn autistic.

Role of food allergens/sensitivities:

From the Department of Biochemistry, Birmingham University, United Kingdom, Dr. R.H. Waring, along with B.A. O'Reilly, coordinator of the Allergy-induced Autism Support and Self-Help Group is doing some exciting work (pending pub.). They are currently carrying out studies to see if children with known food/chemical sensitivities, along with autism, have a deficiency of phenolsulphotransferase-P enzyme and/or a low capability to oxidize sulfur compounds. From the results they have obtained so far, all 18 children showed to have a low enzyme level, and some had little capacity to oxidize sulfur compounds. Now, after 40 children have been tested, the results show the enzyme is low in every child. This enzyme is necessary to metabolize amines and phenols. So it makes sense that with a reduced level children will not be capable to fully metabolize chemicals and foods that contain phenol. Autistic children typically have adverse reactions to many medications. Sedatives keep children awake, antibiotics worsen behavior even anesthesia may be a problem. Equally, a build-up of substances such as dopamine, serotonin, and noradrenaline is possible as amines are also metabolized with the same enzyme. As it is well documented that high serotonin levels are found in some autistic children, if other body chemicals build-up they may be metabolized and produce a substance similar to phytoxins (plant toxins). In unpublished results Dr. Waring ran blood tests on 14 children and found that all had low levels of sulfate (the substrate which is used by the phenol-sulphotransferase-P enzyme). These results show that there may be a fault in the manufacture of sulfate, or it is being used up by an unknown toxic substance the children are producing. [The test for this enzyme is simple; one administers a dose of paracetamol (acetaminophen) followed by a urine collection test for eight hours duration.] Parents reported feverish, off-color children who's urine output was limited. Moreover, some children were not able to urinate too close to the eight hour point. [Caretakers should be aware of the potential side effects of this drug on autistic children , as it is given freely for minor illnesses.]

Many autistic children have major allergies or intolerances to many chemicals and foods. The main offenders appear to be wheat, cow's milk, and salicylates. Occasionally these reactions may turn into urticaria or asthma, but in the majority of these children the effect is the worsening of autistic-like behavior. Interestingly, family history reveals eczema, migraines (especially in mothers), hay fever, and asthma. These children crave the very thing that does them damage. They do this not only with foods, but also non-food items they ingest, mouth suck or chew (e.g. metal, plastic, perfume, soap, plastic, etc.). Nearly all autistic children become picky eaters at the time they "change," eating only a few different foods and both craving some and avoiding some. Some autistic children begin to eat non-foods items with notable immoderation.

There has been speculation that diet may effect other factors of the body. In a double blind placebo controlled trial[62] children were put on a restricted diet for a period of three to four weeks. The foods allowed were two meats, two carbohydrate sources, two fruits, a range of green and root vegetables, bottled water, sunflower oil, and milk free margarine.[63] The child's preference was taken into consideration, and suspect foods or foods the child craved were avoided. Worsening of behavior was connected to all relapses with reintroduction of foods, except for four relapses caused by cow's milk and two by cheese, which produced physical symptoms only. This trial proved diet can contribute to behavior disorders in children, and that their parents were able to report on a behavior change caused by food that could be reproduced in a placebo controlled trial. Although the way in which the diet works is not clear, allergic, toxic or pharmacological mechanisms may be involved. It is possible that diet (foods) might induce changes in brain perfusion similar to those found by Lou et al. reporting on attention deficit disorder.[64]

Many parents have commented after just the initial food/dietary phase, that their children had become more manageable and more amenable to reason. Some to the extreme of beginning to talk, that did not talk before. One should not underestimate or ignore the potential reactivity of the immune system, and various foods, proteins, peptides, or other sensitivities. If a parent notices a good effect from a diet elimination, effort should be made to support the family in their search for other "logical" exclusions. Again, unless there is another significant jump, "extremes" are usually not necessary or justified. What I have experienced clinically, is that as a child begins to do better, it is easier to judge what throws him/her off. You should be expecting a continuous upswing and if there is a fall back, try to think what did he/she have to eat before the decline. What was done differently? Stay "tuned-in" that way . It is also useful to keep a diary, particularly tracking "off" times.

At the Autism conference in Las Vegas, July 1994, Dr. Luke Y. Tsai presented information on neurotransmitters and psychopharmacology in autism. While identifying and looking at different neurotransmitters, neuroscientists have also found different problems with too much or too little of one or the other. Too much dopamine in the brain's limbic system (the brain's emotion center) , and too little in the cortex (the seat of reason), may cause suspiciousness and an inability to process the information in the rhythms and cues of social interaction. Inhibited children may have excessive levels of norepinephrine. In people with too much norepinephrine everything is pumped up; every stimulation demands a response. The other side of the coin is that a shortage of norepinephrine seems to rob people of the ability to know what's important. Working memory (the part that stores information while the mind considers if it is worth keeping and where to file it) fails without enough dopamine. Altered central dopaminergic function in the midbrain has been implicated in the pathogenesis of Tourette's Syndrome. Shortage of serotonin in the frontal lobes and in the brain's limbic system (where emotions come from) seems to relate to impulsivity; the person may not be able to connect disagreeable consequences or what provoked them. Obsessive-compulsive symptoms may be caused by a serotonergic defect involving the basal ganglia.

Several drugs which either enhance or block the action of neurotransmitters have been looked at in Autism and other neuro-processing disorders.

Haloperidol (Haldol) is a dopaminergic blocking agent
Diphenylbutylpiperdine (Pimozide or Orap) is a dopamine antagonist
Methylphenidate (Ritalin) may enhance CNS catecholamine (dopamine and norepinephrine) release from sympathetic nerve terminals and cause inhibition of re-uptake in the caudate nucleus

Clonidine (Catapres) is a alpha-adrenergic agonist
Trycyclic antidepressants inhibit the uptake of neurotransmitters at adrenergic nerve terminals - this results in an increase of monoamine neurotransmission.
Clomipramine (Anafranil) and Fluoxetine (Prozac) are selective inhibitors of serotonin re-uptake in the CNS
Naltrexone - an opiate antagonist

Also at the Las Vegas conference, Dr. E. Gene Stubbs hypothesized that interferon alpha (INF), a product of many cells, but especially cells of the immune system, may be a major factor in the cause of autism. When INF is given in large doses to children with cancer, the result is that they withdraw and become noncommunicative. These are primary symptoms of autism. Also, children with autism have higher pain thresholds, and elevated endorphins in their cerebral spinal fluid. INF can activate endorphin receptors and is a potent analgesic. In addition, INF has been reported to contribute to autoimmune disorders and allergies. An increased incidence of antinuclear antibodies has also been reported in these children. Children with autism frequently have an impaired immune function: high levels of INF could impair the immune function.

In a preliminary study, 10 autistic children were tested for their level of serum INF. All 10 children with autism had a higher incidence of serum INF than the control adults. Normally, levels of INF are not detectable unless one had an infectious disease or illness. While the levels of the autistic children were high, they were not as high as expected. (Note: My experience thus far has shown inconsistent/scattered levels, with some Autistic children being high, while others are low or normal. Interferon could possibly be a potential marker to distinguish different groups, but is routinely subject to multiple influences.)

Other preliminary evidence suggests that a subgroup of autistic children have elevated levels of other cytokines (INF is considered a cytokine, a soluble substance that is secreted by cells that affects other cell functions). It is this author's opinion, that the "true" pathophysiology lies in these other cytokines, rather than alpha interferon. Research is urgently needed to sort these factors out and open new doors for potentially dramatic therapeutic changes within the next year or two, longer if not pursued urgently and correctly now.

William Shaw, Ph.D., presented Organic Acid testing which showed abnormal metabolites in the urine of autistic children. Closely resembling normal products of metabolism, these metabolites are presumably toxic and may interfere with normal cellular energy production. Also, an increase in the yeast-specific sugars arabinose and arabinitol has-been found.
Several explanations are possible:

a) These metabolites are due to a metabolic block caused by a new inborn error in metabolism analogous to PKU.

b) These abnormal metabolites are produced by systemic or gastrointestinal yeast in the human host due to yeast overgrowth caused by a deficiency in cellular immunity and/or extensive antibiotic use. If so:

1. These metabolites are toxic and may be involved in causing autism and/or worsening some of its manifestations .
2. These abnormal metabolites are produced by yeast in the host but are nontoxic and their presence is insignificant.

c) The abnormal metabolites are fake due to yeast or microbial contamination of urine.

(This last possibility is not very plausible because the normal children only excreted very minute quantities of these compounds in their urine.)

Dr. Shaw's test may prove valuable in the diagnosis and/or treatment choices in autism.

THIS AUTHOR'S CURRENT POSITION ON AUTISM:

It has been my direction to "backdoor" into working with Autistic children (and other learning disorders). While ADHD (Attention Deficit Disorder) caught my interest in medical school and during my Pediatric training in the mid-seventies, we had very few answers, and very little objective data to make decisions on within the field. Therapy was very "symptomatic" with little understanding or knowledge of the physiologic events occurring within the brain. During this time, Autism was considered a psychiatric disorder, with most children assumed to be "untrainable" or "barely" trainable, to have low IQ's, and little reason, if any, for optimism in the future.

In 1983 my wife came down with an undefined illness, marked by recurrent flu symptoms, fatigue, sore throat, cervical lymph glands, *and,* as was ultimately noted by researchers studying my wife and other adults with this disorder, cognitive dysfunction, characterized by short-term memory loss and decreased "processing" ability. While desperately trying to figure out how to help my spouse, and by that time other "mothers" and children within my practice, I took a strong look at the principle of nutritional supplementation and amino acid metabolism. During this time, some Autistic children were referred in from West LA. To my surprise, upon testing they had "Candida" titers higher than most patients I was evaluating at the time, and Amino Acid profiles with many similarities to those I was seeing in other patients, with this "mysterious" new phenomena. As I was already beginning to view this phenomena as "immune system" related, it made no sense based on all previous teaching, What did Autism have to do with the Immune system?

As I began attending and taking part in conferences looking at advanced work on neuro-cognitive dysfunction, NeuroSPECT, other advanced neuro imaging techniques and newer quantitative measurements, there was/is an emerging understanding of the Neuro-Immune axis and the concept of *PsychoNeuroImmunology* (the rapidly developing field concerned with complex multi-dimensional interactions between the immune system and the central nervous system). These discussions and presentations raised the idea within me what if a more extreme version of this was "Autism"? The idea of Autism being linked to a severe Neuro-Immune Cognitive Dysfunction is logical, one can say more than probable, at this point.

In addition to the articles noted above, there are many papers already in the literature, noting various immune abnormalities or potential markers. With each passing day, there is less reason to doubt the potential significance of this for "Autistic" syndrome children (?? all or some) and probably other cognitive learning disorders. While metabolic factors certainly play a role in these children, and need to be approached and understood far better than they are now, it is extremely unlikely that the *origin* of this dysfunction lies in a metabolic/genetic defect as we currently understand them. At this time, I would propose that these metabolic abnormalities are secondary to a dysfunctional body. [A process affecting the mitochondria (energy factories) of potentially all cells in the body.] It seems likely that the linkage here is a dysregulated immune system, and the effects created by "out of control" cytokines. As noted above, the ultimate origin or etiology may lie anywhere from genetic factors, a "genetic disposition", to viral, retro-viral, or "other" environmental factors. The good news is that patients do not need to wait years for these answers to emerge, and then years longer for testing of potential agents to develop/occur and gain approval; thanks to research of the last 10 - 12 years there are agents developed as "immune-modulators' which can "adjust" various cytokine levels and other factors. However, these newer, generally extremely safe pharmaceutical agents, cannot be used without first establishing a "justified" population to try them with. While the literature and my personal experience and observations supports without question the concept of an "Immune Dysregulatory" dysfunction within Autism, there exists no solid, medically valid publication, showing "controlled" differences in Autistic Syndrome children.

Within my own practice, in running a series of tests including Immune markers and general function, viral titers/exposure, general chemistry and metabolic markers, one sees informally the branching of this group of children labeled "autistic" into at least 3 patterns, maybe more. It is important to define appropriate metabolic and immunologic markers/parameters, so that we might better separate and understand children's different response to therapy, etc.

In reality, most "anecdotal" reports of "successful" therapies for autistic children can be understood through the concept of a dysregulatory Immune

System and/or altered metabolic sensitivities and dysfunction. In fact, I would dare say that the only unanswered question in this concept is whether one will be able to correct all neuro and metabolic abnormalities via "Immune-Modulator Therapies", or whether there will be a need for combined Immune and Metabolic approaches over time.

Seeing children make dramatic cognitive progress on modified Elimination diets, anti-fungal therapies, and anti-viral/immune active therapy heightens the urgency to move forward into controlled trials with definable markers. With the recent recognition of the fact that if the brain "misses" certain stages of development, you may never make that up fully in the future, the urgency of helping these children can not be overstated. As noted above, we can "accelerate" the medical/therapeutic process greatly, but only if approached with the correct resources and manner. In the meantime, there is some logic worth following in approaching a child therapeutically at this time.

To start with, it's always best to start with the concept of removing "negatives", clearing away "debris". In that position, removing potential food sensitizing agents makes sense, as any agent/protein stimulating a negative immune reaction in the body will create more CNS dysfunction, via the Neuro-Immune pathways. It is logical to attempt to normalize a child's nutritional state, and often, since one is looking at a "stressed" body, there is logic in providing extra nutritional supplements.

As a pediatrician, I feel it is very important and logical to provide and replenish the bodies basic nutrients. However, at present, parents must approach this area with skepticism and caution. There are no controlled trials showing appropriate dosing or long term safety of many "harmless" agents. While there is logic in the concept of nutritional, "supportive" approaches, there are dangers and there are product concerns (re absorption, purity, over-dosage, etc.). Any nutritional manipulation in children is open to dangers or new/induced metabolic problems, vs. potential gains. It has been this authors experience that megadosages usually seem to provide little if any gain vs. risk, and that any "extreme" is subject to many problems in children.

Basic replenishment certainly includes a good basic vitamin / mineral / fluoride supplement, additional Iron, Ca++, Mg++, Zinc++ as indicated, a diet high in protein (the source of natural amino acids, the "building" blocks of the body), low in sugar, good nutritional value, but for the concerns of allergy reactions or sensitivities, best to avoid whole wheat, whole grains, "health-food" store eating. A product such as Nu-Thera, while anecdotal, has been evaluated and observed in a reputable manner, such that it seems a good supplement for most children, with a general caution not to dose at maximum dosing.

The area that a lot of mistakes have been made in, is that of Candida or yeast. Yeast is not the answer to this problem/syndrome. or perhaps any clinical syndrome it is frequently associated with, but seems an opportunistic organism, that can create or accentuate problems in an already dysfunctional host or immune system. You can help a child by treating them for yeast overgrowth or infection, but it and all current therapy should be viewed as a step along the way of getting them better, it is not an answer to the whole problem.

As diet plays a large role in the control of Candida, reducing sugars, wheat products, and other yeast promoting foods is logical within reason. In general, I do not see enough clinical gain to justify "extreme" approaches via diet. There are some children in which "extreme" diet eliminations or adjustments may be logical.

Once basic diet needs are met, there seems good logic, although again very little "hard" medical data, in looking at some type of anti-fungal/anti-Candida approach. (Tests that are being developed may help monitor therapy progress with quantifiable markers in the future.) I prefer a trial of Nizoral (Ketoconazole), using as indicated Diflucan, oral Amphoterecin B, and occasionally Nystatin. While logical to continue if clinically successful, care must be taken to monitor these medicines appropriately, and likely "rotate" around, not stay on any individual medication for too long a time period. Along with medication, it is obviously beneficial to avoid sugar loads (e.g.. fruit, fruit drinks, candies, sugar containing soda, etc.), but, as noted, I do not believe it is necessary or overall beneficial to go to "extreme" diets. Again, follow an approach of common sense. Solving the "yeast" problem is not the answer to Autism, and yet in some children it may be very helpful. Therefore, a therapeutic trial (changing one variable or treatment approach at a time - a critical concept for all therapeutic changes or steps for any child) is justified per the above discussion.

Until "controlled" groups are identified and therapies evaluated, any therapy is anecdotal. I encourage each parent to look upon their child as their own control. It is critical to be patient and allow enough time to thoroughly evaluate an agent for "gains" or "losses" (to this author, one should not continue using any agent which introduce "negative" and should avoid or approach with great caution, any agent with potential negatives). With the appropriate urgency to want to help these children, it is nevertheless a great mistake not to "organize" your approach and proceed logically, with time for appropriate judgments along the way. I would again stress the need to remove identifiable "negatives" if one expects to adequately evaluate "positives".

While there have been many "metabolic" approaches and remedies discussed over the years, there must be a far greater effort at controlled trials before any "special" approach or product can be endorsed. If a parent can be sure of no harm, then cautiously trying some of the products or supplements out there may be useful, but must be evaluated closely on an individual basis.

I have great hope for the possibility of what are called "Immune-modulators". The anecdotal reports of success with DMG (an apparently good product at "low" dosing) and Isoprinosine (?? Success) are examples of agents working via the immune system. Zovirax, an anti-viral agent I have used with some children positive for Herpes viral titers, may be successful via an anti-viral effect, or an unrecognized immune-modulatory effect. As noted, most successful anecdotal therapies are explainable or understandable through the immune system. With acceleration of efforts, it is this author's hope that "controlled" trials with newer, medically developed "immune modulators" might be possible in the near future. Until that point, an overall approach, looking at maximizing the health and function of any individual patient, remains helpful to many children.

While always feeling the overall approach is far more constructive by eliminating negatives, and "positively" helping the body via supplement or immune modulators; once one has done the best possible at present with what is available and useful, there are existing "medications" that may offer help, some of it/them perhaps even "positive" metabolically.

As controversial a term as it might be, Prozac, at low dosages, may have a very beneficial effect on cognitive functioning and sleep cycle (off in so many of these children) via its serotonin mediated effects and by increasing blood flow , particularly in the temporal lobe/limbic system areas. Paxil and Zoloft are in this class of SSRI's (Serotonin Re-uptake Inhibitors) which may be particularly useful in the child who seems to space out a lot, loose focus. On the other hand, the child who comes across as very hyper, if continuing to be so after dietary trials and therapy approaches noted above, may do very well with the help of Catapres (preferably via the patch rather than tablets), or the older children with a low dose of Cylert. Opioid blockers such as Naltrexone may play a constructive role in some patients, but have not been investigated or pursued much by this author to date. While the goal must be "normalization" of the body by directed therapy, some of these agents can be useful if used judiciously and appropriately.

It has been my privilege and pleasure to see many children improve substantially by the above measures. This has only increased and emphasized the need to take these approaches into controlled trials, and to hopefully make possible the introduction of new agents in a very short time. In the meantime, work with a physician or therapist that will work with you and your child. Go slowly, with a concept that when things are better, it takes time for the brain and body to change physiologically. Look for combining and building upon safe approaches and your child's "positive" clinical responses, being careful not to create "negative" effects or to act too quickly to document changes.

Any parent's anxiety and desire "to find the answer for their child" is understandable and commendable, but at this point, slow/progressive clinical observation and trial is the best probability of success, while we hopefully speed up the day of new therapy's and understanding. I might add that this is not a "pipe" dream or need be 5 - 10 years off. Agents exist now that may have tremendous potential to help. They can become available for trial, as soon as medically credible protocols and justification exist. There are a lot of us trying to make this happen.

We all know it is time, we all know it should happen. We need to make it happen, for all of you as parents, physicians, and children.

Michael J. Goldberg, M.D.

Addendum:

Literally, as each day and month passes, we are loosing children who by all recent indications, are both "savable", and likely "recoverable" if dealt with soon enough. At a critical time like this, there is a general slowness in approach, with debate raging louder between Immune and Metabolic schools of thought, and the "no" medical problem thinking of most of "Academics" still. Sadly, much of the accelerated attempt of funding patients are fighting for, will be spent pursuing "more of the same" rather than looking at the new possibilities for the future. At a time like this, with technology and new biomedical advances at our disposal, there is only one way to succeed (I define "succeed" as make advances in therapy for "autistic" syndrome children). If we do not make use of tools and techniques that have evolved in the last five to seven years appropriately, and at academic, peer-reviewable levels, we will never succeed in changing the pace of therapy for these children. Happily, as I know word is beginning to circulate, I am attempting to initiate a controlled cytokine project, in an attempt to open the door for major therapeutic change within twelve to eighteen months (sooner if resources mobilize faster).

There are many advances possible now, but they will NOT occur/succeed unless data and studies are done at a peer-reviewable level (clinically designed and coordinated to speed up the emergence of new ideas, new concepts). Any other efforts will ultimately be more "spinning of wheels".

At the DANN conference in Dallas, January 1995, there was a wonderful coming together of ideas and exciting new directions, but a sad split between "metabolic" and "immune" camps. Also evident was the absolute "distaste" for the mention of academics. I stand strongly behind the convictions expressed above. I would politely challenge anyone to produce a model that has succeeded for any disease in the past, without ultimate evolution and definition by defined studies, acceptable at Academic levels.

Without objectivity, no therapy can be appropriately evaluated, nor will new therapies (already in existence) become accessible. While metabolic vs. immune discussions are interesting, the only major change on the near horizon, will be if the idea of immune-modulators (agents already in existence, but for which we must provide an objective basis to open the doors to their usage) can be tried, and is optimistically successful (many researchers I have been involved with over the last five to ten years, believe success is likely, but remain skeptical till proven). While we "debate" other ideas and options, I believe it is urgent to accelerate efforts to make possible testing of these agents in autistic syndrome children as soon as possible! As noted, with increased discussions already appearing relating to "auto-immune", "inflammatory",origins for "sub-populations" of children, I would propose without hesitation, that "immune-modulating" agents if effective, will be far safer than steroids or other agents now discussed, and needless to say, a better alternative than discussing surgery or severe behavior therapies for these dysfunctional children.

Examining the last ten to twelve years, it has become obvious we are looking at new patterns of disease and illness, that do not fit previously described syndromes, etc. Attending conferences over the last 7 years, being exposed to many "cutting edge" technologies and ideas, one trend emerges. We are looking at a process, appearing to decrease flow/function in the temporal lobe of the brain (other areas may be affected, but the temporal lobe I would propose is the key and common denominator in this process) affecting individuals differently based on their age, and maturation of their immune system. The common denominator making sense through these discussions has been the immune system and a state of "dysregulation".

I would propose to all of you, that while many metabolic and other phenomena, make sense when thought of in a state of or propensity for immune activation/dysregulation, no known pediatric or adults metabolic process makes sense as a model for a "primary" metabolic defect in these children and related patients. Therefore, while we may to some degree help the body metabolicly, develop new markers, and even answer some very interesting questions over the next ten years, we are unlikely to make major medical changes or even approach a cure while focusing on and dealing with what appears to be "secondary" metabolic phenomena, explainable fully by altered cellular metabolism (a fact brought out in many respectable articles over the last 5 years, and accepted at NIH/Academic levels, etc.). This is a dysfunction that is logical secondary to altered cellular mitochondria and immune reactive phenomena. In this light, why are many physicians and researchers trying to "reinvent the wheel", when there are models and evolving technologies explaining all we are discussing logically and with more and more factual physiology. Because, there are still gaps in the above physiologic understanding, basic science will still take (if left alone) probably five to ten years to get into any meaningful therapy discussions. These children do not have "years" to wait.

Dr. Gupta and Dr. Nancy Klimas (Univ. of Miami), are ready to finish and proceed with a protocol to do a controlled study of cytokine levels in "Autistic" syndrome children. These are professors, who if the study is successful, would be unchallenged at the NIH, Academic levels, many have come to disdain. And yet, as I tried to say at the DANN conference and in many other discussions, if we do not move at "Academic" levels, few will listen, and little will really be done. If we do not unite as physicians and patients to speed up funding for at least the basic cytokine project, we are as guilty as the "establishment" at slowing up, rather than speeding up this process.

Potentially worse, as this "epi-phenomena" has grown, there are more and more desperate parents and suffering patients. As noted above, sadly, while there is the potential to bring into play safe, essentially non-toxic medical agents, physicians and researchers are turning to "old" ideas, (i.e. steroids and other potentially toxic metabolic agents) instead of looking at newer and safer ways to treat this phenomena in children (and adults). In addition, while agents like Prozac and Paxil have the ability to actually help the brain if used physiologically (at low dose they can increase temporal blood flow, and work as very mild immune modulators), physicians, as has been done in the past, are using medications at non-physiologic dosages and accepting multiple side effects or partial results, because something seems like a good idea. As much as I have become an advocate of Prozac and Paxil, this has come only after understanding that they could serve a role in normalizing CNS function, and were very safe class B agents if continued. However, I do not believe this or any other currently available agent is going to be successful without an "overall" sound metabolic, nutritional, and immune approach prior to its usage. Likewise, even with the potential emergence of immune modulating agents for therapy, I am not sure whether they will be effective by themselves (as implied by some) or need to be used in a "combined" approach, something that could be designed into controlled trials, if we have the right input and "control" (this is not the usual way Academic's or Drug companies have wanted to design or fund trials in the past).

Watching this "epi-phenomena for the last ten to twelve years, other factors are obvious. If patients are not appropriately identified by scientifically validated markers, we will never sort out or be able to understand the reasons why different patients respond to different agents (pharmaceutical, nutritional, metabolic, etc.). The truth is what we call Autism, ADHD, CFIDS, etc. are all "heterogeneous" populations, in which any drug or therapy trial appears doomed to frustration and failure, without newer, appropriate "objective" markers.

At the Dann conference, the idea that we needed to pursue Academically acceptable studies at peer-reviewable levels, was met with very mixed feelings, and some open hostility. Without this approach, I challenge anyone to tell me how we are going to have significant impact for patients on the medical establishment. In fact, unlike the past, the situation with "restricted" medicine and "fixed guidelines" by HMO and insurance companies, is going to deny care to these children and unless we all help prove the system wrong. Unlike the past, there are ways to do that now that did not exist.

As noted, parents are desperate, reaching for straws, and may be directed or advised into long-term negatives, rather than gain. A metabolic dysfunction by altered cellular metabolism and immune dysfunction, is not likely to correct by any excess of agents introduced to the serum of the bodies. A backup of these agents, may, as noted, be in themselves toxic. Along with others, I have been looking at the idea of an agent called Trental. In theory, it could be an excellent temporary agent, but I have yet to be able to get an answer, regarding long term safety for children. Any therapy proposed must be safe without a doubt. Many of the physicians at the DANN conference had questions with respect to some current therapy usage, and many of us are aware that while some agents may be helpful, some can be toxic, even those called nutritional or metabolic.

To all of you reading this, I apologize for the "personalized" emotion of this last entry, but it has become obvious that with time, many of the negatives expressed above are happening to children, and if appropriate steps do not begin, the future remains ominous for most of these children. While much of "mainstream" medicine remains convinced that many of these children are retarded, it has become evident that at least currently, most of these children are very bright, and their dysfunction is likely a medical problem, unlike any routine disease process in the past, but just as logical, and optimistically, just as treatable.

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[1] Folstein, S. & Rutter, M. (1977), Genetic influences and infantile autism. Nature, 265:726-728

[2] Chess, S. (1977), Follow-up report on autism in congenital rubella. J. Autism Dev. Disord., 7:69-81

[3] Stubbs, E.G. (1978), Autistic symptom in a child with congenital cytomegalovirus infection. Journal of Autism- and Childhood Schizophrenia, 8:37-43

[4] Stubbs, E.G. (1976), Autistic children exhibit undetectable hemagglutination-inhibition antibody titers despite previous rubella vaccination. Journal of Autism and Childhood Schizophrenia, 6:269-274

[5] Stubbs, E.G.,Crawford, M. l., Burger, D.R. % Vanderbark, A.A. (1977) Depressed lymphocyte responsiveness in autistic children. Journal of Autism and Childhood Schizophrenia, 7:49-55

[6] Warren, R. P. , Stembridge, A. M. & Gardner, E.J. (1985) , Deficient immune function of peripheral blood mononuclear cells from patients with Gardner syndrome. Clin Exp. Immunol., 60:525-531

[7] Funderburk, S.J., Carter, J. , Tanguay, P., Freeman, B.J. & Westlake, J.R. (1983) , Parental reproductive problems and gestational hormone exposure in autistic and schizophrenic children. J. Autism Dev. Disord., 13:325-332

[8] Stubbs, E.G., Ritvo, E.R. and Mason-Brothers, A. (1985), Autism and shared paternal HLA antigens. J. Am. Acad. Child Adolesc. Psychiatry, 24:182-185

[9] Peterson, M.R. & Torrey, E.F. (1976), Viruses and other infectious agents as behavioral teratogens. In: The Autistic Syndrime,ed. M. Coleman. New York: American Elsevier

[10] Warren, R.P., Cole, P. , Odell,D. et al. Detection of maternal antibodies in Infantile Autism. J. Am. Acad. Child Adolesc. Psychiatry, 1990,29, 6:873-877

[11] McConnachie, P.R. & McIntyre, J.A. (1984), Maternal antipaternal immunity in couples predisposed to repeated pregnancy losses. AJRIM, 5:145-150

[12] Faulk, W.P. & McIntyre, J.A. (1981), Trophoblast survival. Transplantation, 31:1-5

[13] McIntyre, .A. & Faulk, W.P. (1982), Allotypic trophoblast-lymphocyte cross reactive cell surface antigens. Hum. Immunol., 4:27-36

[14] Boucher J, Warrington EK: Memory deficits in early infantile autism: Some similarities to the amnesic syndrome. BR J Psychol 1976;67:76-87

[15] Hauser SL, DeLong GR, Rosman NP: Pneumographic findings in the infantile autism syndrome: A correlation with temporal lobe disease. Brain 1975, 98:667-688

[16] Waterhouse, L., Fein, D., Nath, J., & Snyder, D. (1984). Pervasive schizophrenia occurring in childhood: A review of critical commentary. In American Psychiatric Association, Diagnostic and statistical manual of mental disorders(DSM-III): An interim appraisal. Washington, D.C.:

[17] Gillberg, C.(1986). Brief report: Onset at age 14 of a typical autistic syndrome. A case report of a girl with herpes simplex encephalitis. Journal of Autism and Developmental Disorders, 16,369-375

[18] Marlowe, W. B., Namcall, E.L., & Thomas, J.J. (1975). Complete Klüver-Bucy syndrome in man. Cortex, 11, 53-59

19 Greer,M K, Lyons-Crews, M., Mauldin, L.B. & Brown, F. R. III. (1989). A case study of the cognitive and behavioral deficits of temporal lobe damage in herpes simplex encephalitis. Journal of Autism and Developmental Disorders, 19, 317-326

20 Hetzler, B., & Griffin, J.(1981). Infantile autism and the temporal lobe of the brain. Journal of Autism and Developmental Disorders, 11, 317-330

21 Jones, P.B., & Kerwin, R.W. (1990). Left temporal lobe damage in Asperger's syndrome. British Journal of Psychiatry, 156, 570-572

22 Courchesne, E. (1991). Neuroanatomic imaging in autism. Pediatrics, 87(Suppl.part 2), 781-890

23 Greer,M K, Lyons-Crews, M., Mauldin, L.B. & Brown, F. R. III. (1989). A case study of the cognitive and behavioral deficits of temporal lobe damage in herpes simplex encephalitis. Journal of Autism and Developmental Disorders, 19, 317-326

24 Ghaziuddin, M. Tsai, L.Y., Eilers, L. & Ghaziuddin N. Brief Report: Autism ans Herpes Simplex Encephalitis. Journal of Autism and Developmental Disorders, Vol. 22, No. 1,1992

25 Ichise M, Salit IE, Abbey SE, Chung D-G, Gray B, Kirsh JC, Freedman M. Assessment of regional cerebral perfusion in 99 Tem-HMPAO SPECT in chronic fatigue syndrome. Nucl Med Comm 1992; 13: 767-772

26 Costa DC, Brostoff J. Ell PJ. Brain stem hypoperfusion in patients with myalgic encephalomyelitis- chronic fatigue syndrome (abstr.) Eur J Nucl Med 1992: 19(8): 733

27 Singh V.K. , Warren R.P. Odell J.D. , and Cole P. . Changes of Soluble Interleukin - 2, Interleukin - 2 Receptor, T8 Antigen, and Interleukin - 1 in the Serum of Autistic Children. Clinical Immunology and Immunopathology 61, 448-455 (1991)

28 Chess, S., Autism in children with congenital rubella, J. Autism Childhood Schizophrenia 1, 33-47, 1971

29 Stubbs, E.G., Ash, E. and Williams, P.S. , Autism and congenital cytomegalovirus, J. Autism Dev. Disord. 14, 249-253, 1983

30 Weizman, A. , Weizman, R., Szekely, G.A., Wijsenbeek, H., and Livni, E. , Abnormal immune response to brain tissue antigen in the syndrome of autism, Am. J. Psychiatry 7, 1462-1465, 1982

31 Todd, R. D., and Ciaranello, R. d., Demonstration of inter- and intraspecies differences in serotonin binding sites by antibodies from an autistic child, Proc. Natl. Acad. Sci. USA 82, 612-616,1985

32 Singh, V.K., Fudenberg, H. H., Emerson, D. and Coleman, M. , Immunodiagnosis and immunotherapy in autistic children, Ann. N. Y. Acad. Sci. 540, 602-604, 1988

33 Toh, G.H. et al. 1985. Proc Nat'l. Acad. Sci. USA 82: 3485

34 Galbraith, G.M.P. et al 1986 J. Clin. Invest. 78:865

35 Toh, G.H. et al. 1985. Proc Nat'l. Acad. Sci. USA 82: 3485

36 Yonk, L.J. , Warren, R.P., Burger, R. A., Cole, P., Odell, J.D., Warren, W.L., White, E. , and Singh, V.K. , CD4+ helper T cell depression in autism, Immunol. Lett. 25, 341 - 346, 1990

37 Warren, R. P., Yonk, L. J., Burger, R. a., Cole, P., Odell, J.D., Warren, W.L., White, E., and Singh, V.K., Deficiency od suppreser-inducer(CD4+CD45RA+) T cells in autism, Immunol. Invest. 19, 245-251, 1990

38 Warren, R. P., Singh, V.K., Cole, P., Odell, J.D., Pingree, C.B., Warren, W.L., and White, E. , Increased frequency of the null

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allele at the complement C4b locus in autism, Clin. Exp. Immunol. 83, 438 - 440, 1991.

39 Morimoto, C., Rheinherz, E.L., Schlossman, S.F., Schur, P.H., Mills, J. A. , and Steinberg, A.D. , Alterations in immunoregulatory T cell subsets in active systemic lupus erthematosus, J. Clin. Invest. 66, 1171-1174, 1980

40 Morimoto, C., Hafler, D.A., Weiner, H.L., Letvin, N.L., Hagan, M. , Daley, J., and Schlossman, S.F. , Selective loss of the suppressor-inducer T-cell subset in progressive multiple sclerosis: Analysis with anti-2H4 monoclonal antibody, N. Engl. J. Med. 316, 67-72, 1987

41 Singh, V. K. , Neuroimmune axis as a basis of therapy in Alzheimer's disease, Prog. Drug Res. 34, 383-393, 1990.

42 Miller E, Rowe K, Bowie C, Judd M, Walker D. Surveillance of symptoms following MMR vaccine in children. Practitioner 1989; 233:69-73

43 Murray MW, Lewis MJ. Mumps meningitis after measles, mumps, and rubella vaccination. Lancet 1989;ii:98

44 Crowley S, Al-Jawad ST, Kovar IZ. Mumps, measles and rubella vaccination and encephalitis. Br Med J 1989; 299:660

45 Ehrengut W. Mumps vaccine and meningitis. Lancet 1989; ii:751

46 McDonald JC, Moore DL, Quennec P. Clinical and epidemiologic features of mumps meningoencephalitis and possible vaccine-related disease. Pediatr Infect Dis J 1989;8:751-5

47 Cizman M, Mozetic M, Radescek-Rakar R, Pleterski-Rigler D, Susec-Michieli M. Aseptic meningitis after vaccination against measles and mumps. Pediatr Infect Dis J 1989; 8: 302-8

48 Forsey T, Minor PD. Mumps viruses and mumps, measles and rubella vaccine. Br. Med J 1989;2:1340

49 Maguire, H. C., Begg, N.t. , Hanford, S.G. Meningoencephalitis associated with MMR Vaccine CDR Vol 1 Num. 6 May 1991

50 Phillips CF. In: Nelson Textbook of Paediatrics. Vaughan Mckay Behrman. 11th ed. Saunders. Philadelphia, 1979:890-3

51 McDonald JC, Moore DL, Quennec P. Clinical and epidemiologic features of mumps meningoencephalitis and possible vaccine-related disease. Pediatr Infect Dis J 1989; 8:751-5

52 Fescharek R, Quast U, Maass G, Merkle W, Schwartz S. Measles-mumps vaccination in the FRG: an empirical analysis after 14 years of use. II. Tolerability and analysis of spontaneously reported side effects. Vaccine 1990; 8:446-56

53 Phillips CF. In: Nelson Textbook of Paediatrics. Vaughan Mckay Behrman. 11th ed. Saunders. Philadelphia, 1979:890-3

54 Communicable Disease Surveillance Center. Virus meningitis and encephalitis. Br Med J 1985; 290:921-922

55 Anonymous. Mumps meningitis and MMR vaccination. Lancet 1989;ii1015-6

56 Nabe-Nielsen J, Walter B. Unilateral deafness as a complication of the mumps measles and rubella vaccination. Br Med J 1988; 297:489

57 R.B.Ashman,J.M. Papadimitrious, A.K. Ott ,et al. Antigens and immune responses in Candida albicans infection Immunol Cell Biol. (1990) 68, 1-13

58 Wilton, J. M. A. and Lehner, T. Immunology of candidiasis Comp. Immunol. 8: 525-559 1980

---

[59] Syverson, R.E., Buckley,H., Gibian, J. et al Cellular and humoral immune status in women with chronic Candida vaginitis Amer. J. Obstet. Gynecol. 143: 624-527 1979

[60] Witkin, S.S., Ing Ru, M.S. and Ledger, W. J. Inhibition of Candida albicans-induced lymphocyte proliferation by lymphocytes and sera from women with recurrent vaginitis. Amer. J. Obstet. Gynecol. 147: 809-811 1983

[61] Kirkpatrick, C.H. Chronic mucocutaneous candidiasis. Antibiotic and immunologic therapy. Ann. N.Y. Acad. Sci. 544:471-480 1988

[62] Carter, C.M. , Urbanowicz, M., Hemsley, R. , Mantilla, L. , Strobel, S., Graham P.J., and Taylor, E. Effects of a few food diet in attention deficit disorder. Archives of Disease in Childhood 1993;69:564-568

[63] Carter CM, Egger J, Soothill FJ. A dietary management of severe childhood migraine. Human Nutrition: Applied Nutrition 1985;39A:294-303

[64] Lou HC, Henriksen L, Bruhn P. Focal cerebral dysfunction in developmental learning difficulties. Lancet 1990; 335:8-11

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PEDIATRICS & YOUNG ADULTS
ADHD/ADD - LEARNING DISABILITIES
IMMUNE DYSFUNCTION
AUTISM

"Autistic Syndrome" A Medical Problem

The New Definition of Autism

Autism as classically defined was and is a devastating disorder. It was a severely incapacitating disability that was relatively rare. It occurred in approximately 1-2 infants per 10,000 births.

In this severe form of "Classic Autism" effective speech was absent. It could include symptoms of repetitive, highly unusual, aggressive and self-injurious behavior. Those afflicted had extremely abnormal ways of relating to people, objects, or events. Parents noticed that something was "not right" generally within the first three to six months of life. These children did not coo or smile. They resisted affection and did not interact normally.

In the last decade, another type of autism has surfaced that is often referred to as "Autistic Syndrome." Children suffering from this disorder generally appear ***normal in the first 15-18 months of life***. They do not present signs or symptoms pediatricians or neurologists would find atypical. These children create an inconsistency with previous held beliefs that 70-80% of autistic children are mentally retarded. They crawl, sit up, walk, and usually hit normal motor milestones on schedule. Up until the age of onset, they are **affectionate** and appear to have above average **intelligence**.

Children with this autistic syndrome may begin to develop some speech but then, without warning, cease to progress, or begin to regress. Suddenly, these children become withdrawn. They are quiet sometimes and hyper at other times. Often self-stimulatory behaviors (i.e. arm flapping, rocking, spinning, or head banging) develop. In time, some manifest symptoms that are both similar and atypical to children previously diagnosed as "classically autistic."

While training as a pediatrician, I was told if I saw one autistic child in a lifetime of practice it would be one too many. What I am seeing today is not the ***autism*** I learned about in medical school twenty years ago. What was once a relatively rare disorder is now twenty times more likely to occur. Before, "autism" was 1-2 per 10,000 births. Now, current statistics suggest a frequency of 20 per 10,000 births (rates of 40 per 10,000 or higher have been suggested).

In the past, autism was considered a "psychiatric" disorder. We now know that autism is a medical condition, not a mental disorder. Perhaps one of the reasons no one has come up with an answer for autism is the way we have thought of it (or rather did not think of it in medicine).

Most "MD" researchers did not look for the answers to autism because they felt this was a disorder that was untreatable medically. Treatment for this affliction was primarily left in the hands of psychologists and a few psychiatrists.

"Autistic syndrome," though still treated mainly by psychologists and psychiatrists, is also no longer considered a psychiatric disorder. It is a biological disorder that requires medical intervention. Physicians are now just beginning to understand the medical origins as well as the actual and potential treatments for autism.

Even though I believe children with classic autism might be helped medically as our knowledge of the brain's physiology expands, for now it might be helpful to separate children afflicted with autistic syndrome from those with classic autism. As children with autistic syndrome increasingly become categorized as a **"medical"** problem, separating them from the many negative connotations and hopelessness associated with "classic" autism could be advantageous to promoting research and funding to help these children. The differences between the two groups may be summarized as follows:

Classic Autism

- A rare disorder affecting 1-2 children / 10,000
- Some/many individuals may have early signs of neurologic injury
- Some may have "physiologic/immune" factors / variables, "treatable" medically by current and future immune medicines
- Generally "abnormal" early (i.e. 3 - 6 months of age)
- "Classic" Autistic symptoms / presentation
- Presumed "static," / unchangeable

Autistic Syndrome

- An increasing population of children with "Autistic/ PDD" behavioral characteristics
    - Current estimate 20-40 children / 10,000 (incidence may be as high as 1-5% of the population based on estimates for chronic fatigue syndrome in adults)
- Does NOT have "objective" physical signs of neurologic damage / injury
- Majority (?? All) are immune mediated, appropriately looked upon as a medical dysfunction - open to potential medical therapy
- Generally "normal" early (usually until 15 - 18 months of age)
- Atypical symptoms
    - Asperger's

  - Landau Kleffner's
  - ADHD / ADD variants
- A potentially progressive disorder (if not treated / corrected)
  - May explain the origin of many cases of "Landau-Kleffner" syndrome

Autism and the Immune System

I have been in clinical practice for the last twenty years. When my wife developed an "unknown" chronic illness in 1982, I began to explore and research neuro-cognitive dysfunction and immune dysfunction / dysregulation in an effort to help my wife. Eventually she was diagnosed with Chronic Fatigue Syndrome, to what is now CFIDS (Chronic Fatigue Immune Dysfunction Syndrome).

The first suspicion I had that autism might be immune-related occurred in 1985. I was in the middle of exploring various alternative therapies in hopes of helping my wife and others afflicted with CFIDS. About the same time, some autistic children were referred to me for evaluation. These children had never had any blood work-ups because no one thought of their "problem" as a medical one. Much to my surprise, they had similar profiles on amino acid screens as the adults I was seeing with CFIDS. *I couldn't help but wonder* ***"What did Autism have to do with the immune system?"***

The Causes of Autism

With the relatively new thinking that autism has medical origins have come several theories. Some doctors believe autism is a result of a metabolic, enzyme, or genetic defect. Although a few children may suffer a built-in genetic or functional defect present since early gestation, I do not believe this is the case for most children afflicted. In addition, the old theories do not fit or began to explain the large increase in the number of children diagnosed with autism today.

I believe "Autistic Syndrome" probably is a state of dysfunction induced in the brain by a dysregulated immune system. It could be possible that this dysfunction may occur in individuals that have a genetic predisposition. This predisposition is somehow triggered by various stresses placed on their immune systems. It's severity varies with the individual and age of onset. The triggers may be different (or similar) in each child.

If it is looked at in relation to the causes of blindness, it is easier to understand. There are many people who are blind but the cause of their blindness is very different. This is consistent with the idea of an immune dysfunction / dysregulation. For whatever the reasons (genetic, environmental, a combination of viruses, etc.), I believe what is occurring is an immune mediated, abnormal "shut down" of blood flow in the brain and therefore central nervous system function. In adolescents and adults, this dysfunction manifests itself as CFIDS and various other atypical auto-immune disorders. In older children, it is seen as variants of ADD (Attention Deficit Disorder) / ADHD (Attention Deficit Hyperactive Disorder). And in younger children/infants, it appears as autism, autistic syndrome and PDD (Pervasive Development Disorder).

When these children are given a NeuroSPECT (a test to measure blood flow to various parts of the brain) and clinical blood work, this connection becomes more than reasonable, it is logical.

The theory that much of autism / PDD is probably an immune-mediated auto-immune disorder is gaining rapid acceptance. It explains the progressive process of the autistic syndrome that occurs sometime between 15-24 months of age. The dysfunction / lack of blood flow eventually leads to injury of nerve cells, which explains the abnormal brain waves, and the large numbers of autistic children suddenly being labeled as "Landau-Kleffner."

The multiple metabolic, physiologic, and immune markers that are abnormal in these children, "make sense" when you think of the bigger picture and consider the primary cause of autism as immune dysfunction, creating multiple cellular / mitochondrial dysfunctions. A distinction often misunderstood is that dysfunction starts out of the immune system, not out of casein, gluten or other metabolic sensitivities. Children with autism have a lot of metabolic abnormalities, but that is a result of the problems with their immune systems.

If a metabolic dysfunction were the cause of a disorder, correcting it would eliminate the disease. If casein or gluten caused autism, eliminating them from the child's diet would cure them, but that does not work.

If metabolic dysfunction is a secondary factor of autism, you rarely, if ever, are going to have a patient recover, by treating the "secondary" rather than "primary" problem. Similarly, if it were true that adults with chronic fatigue have a metabolic defect, how come most of them were normal and generally high functioning for years?

In medical school I was taught to, *get to the reason*, and to *get to what's underneath it*. It's important not to just treat a symptom, or what appears to be on the "surface," but rather it is necessary to treat what is causing the problem.

Medical Treatments

Most of the children I see have healthy bodies with reactive and volatile immune systems. The first step, is to check functioning of various systems in the body. Unless another "medical" problem is found, the immune system is what is creating the misbalance / dysfunction in the brain.

Unfortunately, new, potentially safe immune modulators (steroids, IVGG, are old immune modulators, neither generally safe or effective with this type of immune disorder) are not yet available. Until these immune modulating drugs are scientifically tested in controlled studies, the way to help these children must focus on an overall approach using efforts / steps and medicines available now. By the time a child is referred to my office, their immune systems have not been functioning well for a very long time. This dysfunctional process did not occur overnight and it takes time to "cool" down / help "normalize" the body and the immune system.

The closer you can bring the body towards normal, the better the chance that the body may shut off this reactive and dysfunctional immune system. It is a difficult and complicated process to make the body heal itself especially after years of dysfunction. But if you remove some of the "offenders" that cause the immune system to fire when it shouldn't, you're making it easier for the body to normalize.

The Role of Allergens and Diet

I usually begin by testing the blood to determine allergies that could possibly trigger the immune system to react. Often autistic children come up allergic to a large number of foods, not necessarily because they are actually allergic, but rather because their immune systems are so "revved-up," they react to everything.

This reaction may or may not occur as a traditional allergic reaction of asthma, a rash or hives. But what does occur is an immune mediated, abnormal "shut down" of blood flow in the brain that affect the language and social skills area of the brain and central nervous system function.

I generally start to improve the immune system by placing the patient on a diet free from dairy products, chocolate, and whole wheat. The reason for this is to help reduce the stress on the immune system. If dairy, chocolate and whole wheat are taken away, 96 - 98% of probable "food" allergies are alleviated. However, I do not believe that you can correct this condition by diet alone. If this were possible, parents (and physicians) by now, would have heard of multiple, "unbelievable" successes over the years. Reputable "institutions" would be conducting clinical trials to investigate the "successes."

Since nutritional therapies have not resulted in cures, or even published reports of significantly improved cognitive function, it is illogical, in fact potentially detrimental, to put these children on extreme diets. However, sometimes these children put themselves on extreme diets by only eating a limited number of foods. I don't think there are a lot of normal children who would be healthy on some of the diets these kids put themselves on.

For most of the children, all that is necessary is to eliminate the "main offenders" in their diets that will cause the immune system to react. It is not necessary to eliminate all wheat. Some doctors and homeopaths recommend the elimination of all gluten and wheat. I think these children show improvement because when they are put on a gluten / wheat free diet, they no longer eat ***whole*** wheat. Usually, all that is really needed is to eliminate whole wheat and other ***whole*** grains (due to allergenic potential) from the diet.

I do not normally focus on casein beyond eliminating the primary milk products. Because even though they may, in theory, play a slight role in the background, if the allergies overall are lowered, it will decrease the immune system firing off.

It does not matter if "allowed" processed products are used, as long as they do not appear to be a "trigger." But, avoiding the "main" offenders is extremely important. Eliminating too many products from a child's diet, increases the risk of disturbing a child's metabolic balance, rather than helping to normalize it. *(Note: Many supplements meant to compensate for the diet extremes, may in themselves have allergenic components, acting as negatives triggers to the immune system and the child overall. They may fail to be properly absorbed or contain dangerous impurities. Children may be at far greater risk* *from diet and "supplements" than any perceived risk from properly used pharmaceuticals.)*

The G.I. tract is loaded with lymphocytes (white blood cells that fight infection and disease). Those lymphocytes communicate with the brain. What has always made sense and is "logical" is if the body is sensitive to milk protein and whole wheat protein, coming into the G.I. tract it could cause the immune system to fire.

As research evolved, it was found that milk and dairy can actually cause a microscopic blood loss in the intestine by a "reactive" inflammation of the bowel. It is interesting to note that most of the world's populations get violently ill when given cow's milk. Apparently, it's not a normal human trait to digest the cow's milk proteins.

Asian people have much healthier arteries than we do. One of the major assumptions for this is that they eat soy protein instead of dairy protein. Dairy is the number one source of cholesterol. The entire family can be helped indirectly if milk is eliminated from the meals.

Parents often worry if their child is getting enough calcium. Soy and rice milk often have calcium and vitamins A and D added. However, if a child (girl or a boy) is eating a normal diet, they will get enough calcium.

In the teenage years, girl's diets should be supplemented, if you're not giving them a lot of dairy. But usually, this is not necessary in these first three or four months. As time goes on a calcium supplement may need to be added. Often I will suggest Tums®. Tums® are a very safe source of calcium for a child and they taste good.

Inter-related is the fact that many children and adults who are sensitive to milk but still continue to drink milk products, often have iron stores that are low. Their Hgb. / Hct. are chronically on the low side of normal, even if they were not truly "anemic." This is typically because of a microscopic blood loss occurring through this "inflamed" mucosa.

If dairy and milk were eliminated from the diet, and then a biopsy of the intestine was done, the mucosa (the mucous membrane that lines a structure e.g. mouth and lips) would look normal. If milk and dairy were then reintroduced, the mucosa would look raw and inflamed. (Therefore, in approaching the idea of "leaky" gut, helping the body by removing negatives, is more important than "supplements" and nutritional "fixes.")

As a pediatrician it has been fairly routine for me to see a child do well on formula (even a cow's milk based one) for 12 months, but when the child is switched to real milk, the child experiences congestion, stuffiness, upset stomach, and a whole realm of symptoms not seen before. Whole protein, *unprocessed* food is much more allergenic and has a higher incidence of causing the immune system to react.

The truth is, there is not as bad an allergic reaction out of a processed product. When a food is processed, the protein structure is changed. So a child that might go berserk on milk... may not have a reaction to "processed" cheese. When the protein structure is changed, the food will not give as large an allergenic reaction.

Products from the health food stores are not necessarily the best for autistic children because they are less processed and more pure. They have a lot of whole wheat and grains. For these kids, the cheapest white bread (without milk, whole wheat, or whey) is often the best choice.

To illustrate how peculiar the immune system is, when parents seen the results of the food test come back, a routine phone call is, "How come you did not say 'no eggs'?" You'll almost always see egg white and egg yolk with very high numbers, and yet I will usually say "ignore it." The reason being, unless a child has eczema where yolk or egg are triggering off a skin reaction, for some reason the immune pathway fired off by eggs doesn't seem to play a role in what we are talking about in the brain. I rarely have to worry about taking a child off of eggs, even though you may have this "huge reaction" on the food "screen." This illustrates how parents need to become aware of what doctors have known and "fought" about for years, there is no "perfect" food test / screen, results must always be interpreted in their clinical context. Too often, parents are being "guided" by interpretation of food and metabolic screens that do not have the capability to do what the parents wish. Many mistakes are potentially being made, that may be "metabolically" and physiologically hurting these children.

Although processed food might give a lesser reaction, the importance of avoiding allergens cannot be stressed enough. In the beginning, it is especially important to avoid foods that might trigger the immune system. If the immune system is triggered, the body is affected for a minimum of a week to ten days (or longer). So it's necessary to be particularly strict at the start of the treatment, when the goal is to cool down the immune system.

If it comes down to choosing a food (cheat) with milk or sugar, choose the sugar. From the sugar the child may get hyper for a few hours, but it wears out of their body relatively quickly. From milk protein or other allergens, the immune system can be affected for up to two - three weeks. However since sugar feeds yeast, it is a good practice to minimize sugars in general.

It is also important to encourage the children to eat more protein. This will help balance out their own amino acids, which in turn will help alleviate some of their problems. All these children need protein. It is also necessary to restrict the starches. Healthy breakfasts, lunches and dinners should be served.

Sometimes this process of restoring the immune system to normal can be very deceptive. The child is doing extremely well, and appears almost well or "cured" to a parent, when everything suddenly falls apart.

A child may appear to be well, but unless the body has shut off this process, they still have a reactive, volatile immune system in the background. Even if a child is functioning at a extremely high level, a child should not be regarded as "cured", unless the immune system has truly returned to normal.

While a few rare children will actually outgrow this process, especially if you have taken steps to help normalize their bodies; realistically, it will probably take the advent and usage of new drugs that are immune modulators, to truly shut-off their dysregulated immune system.

This treatment needs to be thought of on a continuum. The closer the child gets to normal, the better the chance that the body may shut off this process. But unless you've gone that last little step, unless this process shuts off, it must be assumed that the immune system is still volatile and potentially reactive.

The only principle I have continued to find logical over the years, is the idea that I'm trying to just help a child "normalize" their body (and brain). Can I help them balance out their body? If I can change the diet, their own body can help balance itself. There continues to be no evidence in these children of any pre-existing, built-in enzyme or metabolic defect. Therefore, by focusing on the overall intake, encouraging more protein, less starch, a child's body will help balance out and replace needed amino acids (the building blocks of the body) and other nutrients.

With rare exceptions, I will never say don't do something if you truly see a child do better and it's safe, but in most cases I have found that you can get to the right point if you just think of it as cool down the body's immune system, help "safely" where medically and nutritionally possible, and extremely important, avoid offenders or triggers. If a child is doing better and their allergy test said they were not allergic to apple, but you give them a drink of apple juice and the child is bouncing off the walls, it doesn't matter what the test said, that child should not have apple juice. And this is the way parents have to work with their own child.

Until new immune modulators are tested and ready for use with patients, I regard each step of treatment as an attempt to help "cool-down" the immune system, and help the body "adjust" itself in a healthier manner. While the principles are becoming very consistent, each child (his/her body and brain) must be "individualized."

Candida or Yeast and Autism

While taking the risk of opening a medical controversy, this author certainly believes there is a logical connection between yeast and a dysfunctional immune system. However, this theory is not *yet* widely accepted by the medical community, but over the last few years has become easier to talk about and "discuss". Candida is a yeast-like fungus that is present in all our bodies. Presumably, yeast / Candida is in every normal G.I. tract. That is where the confusion begins.

Normally, a healthy immune system keeps the yeast in check. If the immune system is not working properly, the yeast have a chance to overgrow and become a problem. Yeast is one of the likely pathogens contributing to a metabolic imbalance that is a ***secondary*** result of a dysfunctional / dysregulated immune system. It is NOT the *primary* reason or cause for autism.

There is logic in saying that if an immune system is dysregulated, a secondary problem potentially due to Candida needs to be treated. Some doctors hypothesize that autism is caused by a "leaky gut." With this theory comes the assumptions that withdrawing allergens and treating a yeast overgrowth, will help the GI tract to return toward normal. The problem with this thinking is that if yeast is not the cause of autism or PDD, then treating Candida is not going to end the autistic or PDD state. I believe it is only one of the many steps needed to help normalize the body.

Many children afflicted with autism have had frequent ear infections as young children and have taken excessive amounts of antibiotics. This has exasperated the yeast problem in these children. Other possible contributors to Candida overgrowth are hormonal treatments (i.e. steroids, BCP pills, ?? secondary exposure), immunosuppresant drug therapy, exposure to herpes, chicken pox, or other "chronic" viruses, or exposure to chemicals that might upset the immune system. There is an increased probability, that a "general" environmental factor affecting our immune systems (i.e. ozone layer depletion, "toxic" chemicals, etc.) may be operative, affecting many children and adults.

Because it is impossible and not practical to expect anyone to stay on a totally yeast-free diet, ongoing medication, anti-fungal supplements, and avoidance of dietary negatives are necessary to control Candida. Even with the use of anti-fungal drugs, it is still important to limit sugar when there is a yeast problem, because yeast grows 200 times faster in the presence of sugar.

If a potent anti-fungal such as Diflucan or Nizoral is used, it can be assumed that within 1 - 2 months most all of the yeast will die off. I do not use Nilstat or Nystatin. For most children Nystatin is ineffective. And yeast, like bacteria with antibiotics, have become resistant to Nilstat (and other antifungals).

Usually, I will use Nizoral or Diflucan for about four to six months while trying to alleviate other stresses on the immune system and "maximize" a child's function. In 7- 12 days some patients experience "die off." This is the *only* time, a "negative" reaction to a medication can be a good sign. When the yeast is being killed one experiences either a "sensitization" reaction to "products" of the yeast being killed, or there is release of "formaldehyde" like products or other potentially toxic derivatives, that can contribute to negative symptoms in a patient, including bouncing off the walls, miserable, and irritated. I know it is ironic, because it actually is a good sign that the child has a yeast problem that can be corrected with medication.

It is important that the parents check in during "die-off" so I can be sure what is occurring is indeed die-off and not a reaction to the medication. Die-off usually lasts about 7-14 days and after that time the change in the child can be rather dramatic. If the die-off does not end in 14 - 17 days, it is generally a reason to change choice of anti-fungal.

If the treatment is successful, usually eye-contact improves. The children seem more tuned in and less "foggy." Parents report that after the yeast is under control the frequency of inappropriate noises, teeth grinding, biting, hitting, hyperness, and aggressive behavior decrease. The children no longer act almost drunk by being silly and laughing inappropriately.

While on Nizoral or Diflucan, I have the patient take monthly blood tests to monitor liver function before any damage might occur. I tend to be on the cautious side, "officially" testing is recommended every 2 - 3 months.

I change medication at six months, though in theory one could go longer. The reason I stop at six months is because Nizoral has a very mild effect on the adrenocortical axis. It's part of the internal steroid mechanism. While this may even be part of how "Nizoral" helps the body, it also limits how long one should be on Nizoral. Generally, I will try to switch to Amphotericin B, which has recently been licensed as an oral liquid in this country, can now be legally compounded by certain pharmacies in the U.S.

If the antifungal therapy is stopped completely, and the body's immune system has not returned to normal, the yeast will return. Ultimately, the key is the body's own ability to keep in check an organism that it doesn't want to have there to start with.

Some doctors mistakenly give medication to control the yeast for only a few weeks or even a month. Then the treatment is stopped because the child is doing better. The problem with this kind of therapy is that if a child is helped for a short time and then the treatment is withdrawn, the yeast is going to come back, perhaps even as a stronger, more resistant strain. Whereas if the treatment took that child to normal, and their immune system became normal, it would be possible to withdraw all treatment and the child would remain healthy.

Antivirals

If the blood work suggests that a herpes related virus or "unidentified" retro-virus might be in the body, a therapeutic trial of the antiviral drug Zovirax is given. The only thing (in theory) treated with Zovirax is a herpes related virus. If a virus is present and it is gotten under control, it's one of many major steps necessary to help the body and the immune system.

On a few of the older children I am now starting to use Valtrex, which is an improved version of Zovirax. I never recommend something for a child unless I can say, "It is safe."

When herpes virus is discussed, we all think of cold sores, vaginal sores, but may not consider chickenpox, CMV (cytomegalovirus), or Epstein Barr. These are also herpes viruses. Being in the herpes family, they have the unique ability to sometimes stay around even after the overt symptoms are long gone. They hang around the body and live in the nerves. Perhaps a "new" Herpes related virus or retro-virus may be playing a role in some of this epiphenomena. However, at this time we do not have the technology to explore and understand how all of this works.

Selective Serotonin Reuptake Inhibitors (SSRI's)

The only medical agent out there that's routinely available and directly seems to help the temporal lobe are called the SSRIs, Selective Serotonin Reuptake Inhibitors. The drugs that come under this category are Prozac, Paxil and Zoloft. What these drugs do is, for the first time, work on a *specific* pathway in the brain. They block the reuptake of the serotonin released.

If the serotonin released "stays around longer / more effectively," part of the brain works better. Prozac may also alter part of the "neuro-immune" axis, working to increase blood flow and function in the temporal lobe. This increased blood flow and improved function of the temporal lobes, helps many behavioral and processing problems in these "autistic" children. By helping restore and preserve temporal lobe function, one may be helping maintain a ***healthier*** brain.

Importantly, this is not an effort to control the children with medicine. A very small dose, usually 2-4 mg, is used with a four or five year old. If controlling a child's behavior was the goal, a dose of 10 - 20 mg would be used. Instead all that is needed to help function in the brain is a very small (but *consistent*) dose.

The purpose of using these drugs is an effort to get a child's brain to work better. In the past, if you talked about an antidepressant you were thinking Valium, Librium, Phenobarbital, that's how you "calmed" someone down. That's not what you're doing with Prozac, Paxil or Zoloft. Pharmaceutical companies are trying to design drugs that will help the brain more physiologically than the agents out there did before. SSRI's represent the first of new "designer" drugs, with the capability of acting physiologically within the brain.

These drugs ***can*** help a child medically to function better. They help transmitter effect and likely increase blood flow to the area of the brain that was not functioning properly before. And if the brain starts working, the results with these children can be phenomenal. These children are usually extremely bright. *(Note: While capable of helping medically, this author believes strongly that one cannot judge their positive effects, avoiding negatives at low dosages, without controlling / combining diet and other steps at the same time.)*

Immune Modulating Agents

There are agents that have already been tested and developed, and are now undergoing new usage's testing in adults that will let us ***adjust*** the immune system. Hopefully, they will have the ability to fine tune the body and put the immune system back on track. These drugs are already in existence, but are available only through appropriate research protocols. They could potentially correct all of the processing problems associated with autism (and possibly other childhood learning disorders) where "immune-mediated."

The trouble is, children are the last in line. Even though trials are now starting for adults, no agency wants to test children. The liability is too much. It is only after you've proven things extensively in adults that treatment for a child is even considered. If medicine follows its usual course of action, trials for children would be at least another four or five years away.

That is too long to wait. We must find a way to make this happen sooner. Even if the agents are identified that will "normalize" function or stop abnormalities from occurring in autistic children, these agents must be used before children pass important functional and developmental steps that might not be regained if these agents are administered later in life. Funding for this research is of the utmost importance. We can not lose children to *autism*, who have the potential to lead a normal life.

Even in older children, it appears parts of the brain can be helped significantly. If cognitive function improves, the "equation" for the future changes. But, educators, therapists must start thinking "rehabilitation" rather than just "training." Often it is extremely slow and difficult to sort out compounding behavioral issues (perhaps after so many years of being bright but frustrated and dysfunctional secondary to the non-working parts of the brain).

Vitamins - Nutritional Supplements - Natural Therapies

I do believe the B Vitamin mechanism is off in children with autism (again, secondary to mitochondrial / immune dysfunction, not the primary reason or cause). Perhaps this is the reason that large amounts of Super Nu Thera have not seemed to cause any *measurable* damage. Perhaps a lot of the Super Nu Thera is not being absorbed, and the small amount being absorbed may be helping some children. Some neurologists are worried that if some of these children are absorbing too much it is not healthy. There needs to be controlled trials to determine the correct dosage and real safety or dangers of this agent.

I believe in the product, but I don't believe in blindly giving it to a child. Any agent (nutritional, natural, medical) must be judged on effect (good or bad) and long term safety. It dangerous to push a child's body to any extreme with mega-dosages of supplements. Common sense does not mean "mega" dosages of anything. More is not necessarily better.

Since nutritional factors do not account for the cause of autism, as noted above, it is illogical, and in fact potentially detrimental, to push a child's body, to any extreme with mega-dosages of supplements.

Gamma Globulin

You don't in general cure someone afflicted with autism or CFIDS with IM gamma globulin, but it may play a helpful "supportive" role. Gamma globulin does have its place for various other acute autoimmune processes. Unfortunately, IV gamma globulin, is not the same as IM. With IV gamma globulin, a human product of blood goes directly into the veins, and must be prepared / processed differently than IM (Intramuscular). There is a danger of passing hepatitis and / or any number of unidentified retro-viruses with this type of therapy. Presently we have no reliable screens for hepatitis C (some screening becoming possible), D, E, F, G. etc. If there is an allergic reaction in a child with low IgA, the possibility of either getting very sick or even dying is very real.

This type of therapy has the potential to be very dangerous. Recently, in the Midwest (I believed Minnesota and/or Michigan), there were 12 cases of hepatitis C contracted from a bad batch of IV gamma globulin. This and other risks are not justifiable with such a low probability of "success" with this agent.

There are some people who will get a little better from IV gamma globulin, because once again a dysfunctional immune system is the culprit for these children's problems, and this product can help the immune system. But the trouble is that it is not a sustained gain. Until newer immune-modulators are available for these children, a combined plan of improving the immune system, the body, and the brain, has a much higher probability of success. If you help the immune system, the body will work to repair itself.

Therapy Focus - Goals - Issues

Even if we had that instantaneous answer to normalize the body, a child still needs to be caught up on what they missed and "re-educated." In the past, the focus for autistic children has been on trainability, cooperation, behavior, NOT on improving the cognitive processing. Hopefully, a shift to the idea of "rehabilitation" is already in motion, a full review of techniques and goals is urgently needed.

Sadly, medications or efforts to "calm" the brain and child down, may further shut down the areas we want to improve. What is necessary to ask about every medical treatment or medication is whether it results in a child who is brighter eyed, processes better, functions quicker? Are there negatives associated with what has been prescribed?

The hard part is often discriminating between what is behavioral and what is medical. If you get a change where a child is more tuned in, processing better and literally gives the parents, or the teacher / therapist a "bad" time, that needs to be dealt with behaviorally, not medically.

What I am continually seeing in these children is the better their brain works, the more they act out like a two or three year old kid that never had the "reins" put on them. If that's in the context of the brain working better, it's not a negative.

Clinically, my experience has been to literally watch a young child (below 4 or 5) "pick-up" where their brain development ceased to function normally. They need to go through the same developmental steps all children do, but they are doing it at an older age. They developmentally act like a 2 year old child, but have the body and skill of a 4 or 5 year old.

An older child, can be helped significantly if cognitive function improves, but as noted above, it is a longer *rehabilitation process* and catch up effort. Often it is extremely slow and difficult to sort out the compounding behavioral issues (perhaps this is due so many years of being bright but frustrated with their inability to communicate).

It has now become common practice to hear a parent of a four or five year old tell me that their kid literally is doing things that they stopped doing at two. In these cases this is not regression. It as though you literally turn the brain back on where it stopped at 18 months or two years of age. This is what is expected and is fine as long as you get them through those stages and you help them catch up.

As a child is functioning better and even when they are dysfunctional, they like any normal child need praise, limits and consistency. The problem is that parents are dealing with a child with the physical ability to get into the trouble a five year old child would, but without the lines and limits parents would have set previously for a 2 or 3 year old child. (Note: All children go through *normal* testing phases, where they need to learn what is okay, what is not okay, etc.)

There is a critical time limit for helping these autistic children. If a child does not develop or use certain tracts in the brain, he may never do so. If the child has not used these tracts in the temporal lobe you may never get them to develop "fully." Usually, the younger the children are when you start to "normalize" the body and the immune system, the better the prognosis will be. These kids are young brains, the longer they don't get help, the worse off they're going to be. However, the discussion of "deadlines" must be taken in context by our past (and generally present) inability to adequately measure and evaluate areas of brain function objectively.

There are some physicians who will argue that the body is still "fixable" at eight or nine, but realistically there is a line. It has been this physicians experience to note children up to 5 or 6 will often "turn-on" and pick-up where they stopped, generally about 18 - 24 months old. On the other hand, as children approximately 6 - 10 or 11 improve, it is a slower process, often requiring more "help" to "learn" the basics, grow-up developmentally, and then move ahead successfully.

All of these observations reinforce the fact that we can not wait the normal cycle of 10 to 20 years for medicine to find the answers for these children. If we're going to maximize the probability of success, we still must mobilize efforts to focus on "realistic"/ probable medical solutions available within 1 or 2 years, versus "genetic" therapies, perhaps available in 10 - 15 years.

We must never underestimate the unknown, and the power of the body when dealing with these children. An illustrative case is a physician's child who is now 10 years old. The child came to me literally wild, I mean the parents were that close to realizing they were going to have to institutionalize him. Currently, the boy is now up to a couple of sentences. He is in school and is starting to learn. Although I can't say to these parents that I have the same top hope for a patient who is 9 or 10 that I may have for a 4 or 5 year old, that doesn't mean there can't be a lot of improvement. This child NOW has a good opportunity to develop skills. He certainly is showing he's bright and can learn.

The Image of Autism and Its Implications

Unfortunately since doctors believed autism should be treated by psychologists and psychiatrists there has been an absence of pediatricians in this field. It was and still is believed by noted neurologists that nothing can be done medically to treat these children. Fortunately, as these children are changing with therapy, respected neurologists and other pediatric researchers, are beginning to feel it is time to "take a second look."

Psychologists and behavioralists, sometimes give parents advice based on the assumption that a child with autism is a retarded child who "doesn't know any better". While the advice given is meant to help, these are often bright children that are not being expected to conform to or understand rules and limits. Because of these well-meaning professionals, these children often become a bigger problem behaviorally. Without proper discipline and expectations by teachers and parents, any child will be a problem, these children will be a disaster.

A overwhelming obstacle to changing the image for these children is the failure of tools available to date to "objectively" evaluate CNS (Central Nervous System) functioning, in turn perpetuating the subjective screening tests and procedures currently used. To this day, good researchers often take a position, if they can't measure it, it must not be real. Perhaps, it is far more appropriate to acknowledge there are areas of physiologic and metabolic function that we have not yet developed the tools or techniques to measure, but that does not mean they should be discounted clinically / medically.

As time goes on it becomes more evident by clinical confirmation and research that autism is an auto-immune disorder (see previous review article "Autism and the Immune

Connection"). With this knowledge I have become extremely concerned that some of the previously used drug, metabolic, and psychological therapies that have had little or no history successfully treating this type of disorder in adults, are not likely to be successful in children. In fact, many may be potentially harmful.

It is one thing to try a potentially dangerous therapy or one with many unknown or undesirable side effects on a brain-damaged or retarded child. It is quite different to experiment or operate on children with dysfunctional, but potentially healthy, normal brains.

There is work being done by doctors with medicines and homeopathic therapies, that I am not sure is safe for children. They are prescribing extreme diets and mega-doses of supplements. In part these doctors are correct that metabolic processes in these children are not working properly. But I believe the evidence is mounting daily that they are a ***secondary*** result of a stressed / dysfunctional immune system, NOT the cause of autism.

While some dietary restrictions and nutritional supplements may help to "cool down" the immune system, more is not necessarily better. Often these remedies are given because they will "do no harm." But harm is occurring by the failure to recognize and expedite potential new therapies with immune modulators that could possibly help normalize the immune systems of these kids. And harm is occurring when parents and physicians are using potentially dangerous therapies and even operating on these children's brains with little probability of success.

In contrast, the good news is that children afflicted with autism whose immune systems have been helped are showing they are bright thinking individuals that are not what the world expected. Children with the "label" of Autism / PDD are not retarded. They have normal or above normal intelligence. They are not throw away kids that cannot be helped. They are children who are suffering from auto immune dysfunction that can possibly recover.

But the label of autism still continues to carry old "negative ideas, negative implications," and in turn lowers the urgency and priority to help these children. **It is time to change that label, that image, and the future for these children.**

It is this physician's hope that 1997 is the year of that change. Through focusing and combining efforts, this can happen; for the children's sake . . . . it must happen.

MJG/eg
1/97

Mr. BURTON. Dr. Megson.

Dr. MEGSON. Mr. Chairman, members of the committee, my name is Mary Megson. I am a board-certified pediatrician, fellowship-trained in child development, a member of the American Academy of Pediatrics and on the clinical faculty at the Medical College of Virginia.

I have practiced pediatrics for 22 years, and the last 15 years, I have worked only with children with developmental disabilities, which include learning disabilities, attention deficit hyperactivity disorder, mental retardation, cerebral palsy, and autism.

In 1978, as a resident at Boston Floating Hospital, I learned that the incidence of autism was 1 in 10,000 children. Recent surveys have suggested an incidence in several parts of the country of between 1 in 300 and 1 in 600 children.

Over the last 9 months, I have charts now in an office that I opened last June on 1,900 patients, well over 1,200 of whom have fullblown criteria for autism. I have 70 autistic children in a clinical trial and I am beginning a second clinical trial to look at treatment on these children.

At the same time, the State Department of Education says there are only 1,522 children with the diagnosis of autism in the State of Virginia.

Mental health and mental retardation agencies have scrambled to set up infant intervention programs and have had a hard time keeping up with the numbers of delayed infants and toddlers. I have served as an advisor for the city of Richmond and the surrounding counties as they set up these infant programs and also set up special education programs for children with autism. Now there are autistic classes in each county and several classes in several schools. There has been a very rapid rise over the last several years, The segment of children with “regressive autism”—who develop normally and then regress usually between 18 and 24 months—has increased dramatically. This past week, I was involved in four cases of children who were perfectly normal in their development until they had their school-age shots at age 5—DPT, hepatitis vaccine, MMR. Within weeks, they were autistic. In the past, this was unheard of.

In the vast majority of cases, I have discovered that one parent or another reports night blindness or other rare disorders associated with a defect in something called a G protein. G proteins are proteins inside the cell that join receptors that sit in the cell membrane. They are cellular proteins that upgrade or downgrade signals in their sensory systems all over the body that regulate touch, taste, smell, hearing, and vision. They are important also in turning on or off multiple metabolic pathways, including those for glucose, lipid, protein metabolism. They also turn on and off pathways for cell growth differentiation and survival.

Close to the age of autistic regression, we are adding a second defect to the G protein—namely, pertussis toxin—which completely disrupts these G protein pathways. The opposite G protein pathways are on without the off switch.

In my research, I have discovered that some children are protected if they have the lipid-soluble form of Vitamin A, that’s found in natural sources. Those children, especially those who are breast-fed—get the early vaccines in spite of having the genetic defect and do fine. However, the measles/mumps/rubella vaccine at 15 months of age depletes the body of all Vitamin A. When they get the DPT the same day or several months later, many of these children disconnect.

There are several metabolic problems that I am seeing repeatedly in these children. The pathway to break down the storage form of glucose in the body is on without opposition. These children have elevated blood sugars. In the past week, I have been made aware of four cases of autistic children who developed juvenile onset diabetes. There is a 68 percent incidence of diabetes in the parents or grandparents.

Lipid breakdown is turned on without opposition. I have diagnosed many 2½-year-old children with autism who have serum cholesterol of 240 and above. There is an incidence in one of three of these families of heart attack of a parent or grandparent under age 55 and diagnosed with hyperlipidemia.

Of great concern, cell growth, differentiation, and survival is turned on, which leads to uncontrolled cell growth. In the first 60 families I examined, there were 62 cases of malignancies associated with the RAS oncogene.

I have also discovered that the measles antibody that the body makes, once they are exposed to the measles vaccine, cross-reacts with intermediate filaments. Intermediate filaments are the glue that hold the cells that line the gut wall together, so when they get that MMR vaccine, they develop a leaky gut. Intermediate filaments are also important in areas of high stress. One of the areas of highest stress in the human body is the upper small intestine right below the stomach. They develop a chronic autoimmune disorder at that point.

The loss of the cell-to-cell connection also occurs in the blood-brain barrier and in the cells that surround the bite annicul: where toxins are excreted from the body. So any toxins that they are exposed to, leak through the gut wall, and they cannot pump them out of the body.

The loss of cell-to-cell connection interrupts another process in the body which is very important called aproptosis, or the ability of neighborhooding cells to get rid of abnormal cells. The MMR vaccine at 15 months precedes the DPT vaccine, which turns on uncontrolled cell growth differentiation and survival.

Most families have reported cancers in parents or grandparents. The genetic defect found in 30 to 50 percent of adult cancers is a cancer gene, the RAS oncogene. This is the same defect that is the defect for congenital stationary night blindness.

In Harrison's Textbook of Internal Medicine, which is the standard textbook in medical schools all across this country, it is stated that it is absolutely contraindicated to give the MMR vaccine or a measles vaccine in the face of Vitamin A deficiency. I am afraid that some of these children are facing that vaccine when they are already deficient in their Vitamin A stores, and then they cannot reconnect pathways.

Most of us in our current diets have the lipid-soluble form of Vitamin A taken out. This lipid-soluble form is found in liver, kidney, milk fat and cod liver oil. In lowfat milk products, however, it is taken out, and another, water-soluble form is added which they are unable to absorb.

Mr. BURTON. Pardon me, Dr. Megson.

You heard all those buzzers. That means that I have to run to the floor and vote or else I will be voted out of office, which I do not want to happen.

Dr. MEGSON. OK.

Mr. BURTON. So if you will please bear with me, I will get over there and vote and get back just as quickly as I possibly can, because I am very interested in everything that you folks are saying, and I do want to get answers to a number of questions.

We have two votes, and I will be back just as quickly as possible, so we will stand in recess—there are how many votes—I think everybody had better get a cup of coffee, because there are four votes. It is probably going to be half an hour before I get back. I apologize.

We stand in recess.

[Recess.]

Mr. BURTON. I really want to apologize to those of you who have been so patient today hearing all the debate. It must have been difficult for you, but I am sure it has also been entertaining.

Would you close the doors in the back after everyone comes in?

OK. We left off with Dr. Megson in a very impassioned moment of her talk.

Dr. MEGSON. Briefly, I was saying that in the vast majority of these children, I get a history from one parent or another of a disorder associated with a defect in these major signalling proteins, the G proteins.

As I approached my research, I looked through the eyes of these children and tried to figure out what their world was like. Now that I have talked with them and know what questions to ask these children, I understand how these G protein defects affect their perception.

They have a severe loss of rod function in their eyes. There are four beautiful studies that have been published and out there for several years that show this. They are then left with cone function in which to see their world. Cones give us color and shape in our environment. The only situations I could imagine having only color and shape to organize my world are those "magic eye puzzles," where you look beyond and back up, and then you get a box of 3D. That is the only place in their visual field where they get a 3D impression of objects.

Mr. BURTON. Everything else is flat?

Dr. MEGSON. Correct.

Only then, when they look at a box, like television or a computer, or a therapist who is sitting right in front of them, do they consistently hear the right words for what they are looking at. So that most of the day, they are not hearing the right words for what they are looking at, because they only have one area of their visual field where they see 3D.

I have treated some adults, and one adult I am treating in Alabama calls me every week and gives me the measurement of his "box" as it grows, and he gets better, which is really fun.

The other areas of perception and sensory perception are controlled by G protein pathways as well, and adding a second defect to these children, who on a genetic basis probably have a first defect, changes multiple sensations. Their avoidance of eye contact is an attempt to have light land off-center in the retina, where they have some rod function. So when they look away from Mom, they are actually looking at Mom. When we make them force their pupils directly in front of us, we are making them look away from us. With this form of natural Vitamin A treatment, within days, they look right at you.

The other things that happen in these children—suddenly, Mom's touch starts to feel like sandpaper on their skin because of modulation of touch; common sounds sound like nails scraped on a blackboard. These are words that autistic children have given me as they have gotten better.

We think these children cannot abstract, when actually, we are sinking them into the middle of an abstract painting at 18 months of age, and they are left trying to figure out if the language they are hearing is connected to what they are looking at at the same time.

This defect for congenital stationary night blindness is on the short arm of the X chromosome, which explains the male-to-female ratio autism, and it affects cell membrane calcium channels that Dr. Goldberg just referred to in the hippocampus. These are the NMDA/glutamate receptors in the hippocampus. These pathways are where major pathways processing language cross from the left side of the brain to the right. The pathways then go back through the hippocampus. The frontal lobe is where attention is added, executive function, inhibition of impulse, and all social judgment.

When stimulated, these NMDA receptors through their G proteins stimulate other receptors in the nucleus of the cell, right there at the hippocampus. These receptors were discovered by Ron Evans in December 1998. In the animal model, when they are blocked, the mice are unable to learn or to remember changes in their environment; they act like they have significant visual perceptual problems, and they have significant spatial learning deficits.

Of great concern to me is that when the hepatitis B virus was initially isolated, the protein sequences were isolated and inserted into the gene for one of these Vitamin A receptors, RAR beta. This is the critical receptor important for plasticity and retinoid signaling in the hippocampus in this area of major pathway intersection. We will have to look at the vaccine and see if there is any defect being produced by that related to the recent increase in autistic spectrum disorders.

What I am treating these children with is the natural, lipid-soluble form of Vitamin A. I am giving them their recommended daily allowance only of Vitamin A in the form of cod liver oil to bypass these blocked G protein pathways and turn on these central retinoid receptors.

In a few days, a lot of these children look at me, focus, they regain eye contact, and they talk about their box of vision growing. After 2 months on this Vitamin A treatment, I give them a single dose of a medicine called bethanechol, which stimulates pathways in the parasympathetic system in the gut. What I have discovered is that there are nerve receptors in the gut called acetylcholine receptors, or muscarinic receptors which are blocked in these children. This medication mimics acetylcholine. It does not cross the blood-brain barrier. I give it to these children in the office, and sometimes, 30 to 40 minutes after the initial dose, after having pathways corrected for several months of Vitamin A, when I bring them in and give them this medicine and observe them, they connect in the office. I have had children look at me, talk, act out, talk back to their mothers, and use vocabulary above their chronological age. This is a disconnect, and I have seen this again and again and again. Bill Walsh in Chicago has seen it; Woody McAinnis in Arizona has seen this change.

In one child I have treated beginning last April, her IQ score has gone up 105 points, from 60 to 165.

This treatment improves cognition, but these children are still really physically ill. Their Vitamin A stores are depleted, oftentimes before and if not before, at the time of the MMR vaccine, and they cannot compensate for these blocked pathways.

Vitamin A has been called the anti-infective agent. It leaves them immunosuppressed when they are depleted. They lack cell-mediated immunity. Adding a second defect to this GI alpha protein blocks a very important pathway in the body where you convert retinol into something called 14-hydroxy retro-retinol. 14-HRR is needed to turn on T-cells.

I give these children cod liver oil—cold water fish oil is the only natural source of 14-HRR—and the children get well.

The parasympathetic nervous system which is blocked in the gut is part of what I call the peripheral nervous system. We think of the nervous system as having two major parts. The central nervous system is the brain and spinal cord. The peripheral system is divided into two parts. The sympathetic nervous system is your fight-or-flight response—everything that happens to your body when you run away from danger—you dilate your pupils, increase your heart rate, and increase your blood pressure. The parasympathetic side of the peripheral nervous system allows us to sit back, relax, focus, and digest our food. We are blocking the parasympathetic side of the nervous system, and these children are in fright or flight all the time.

I have asked someone to bring these panels out so you can look at these children and see their faces.

I live in a small middle-class neighborhood with 23 houses. I recently counted 30 children who were on stimulants for attention deficit hyperactivity disorder. One week ago, my oldest son, who is gifted but dyslexic, had 12 neighborhood friends over for dinner. As I looked around the table, all of these children but one had dilated pupils. After 2½ months of taking his recommended daily allowance of Vitamin A and D in cod liver oil, my son announced: "I can read now. The letters do not jump around the page anymore." He can focus, and his handwriting has improved dramatically.

In a survey in his private high school for dyslexic students who are bright enough to go to college, 68 out of 70 of those children reported night blindness. They see headlights like starbursts, and they get a whiteout when their picture is taken.

I think we are staring a national disaster in the face which is affecting thousands of American children. The children with autism, ADD, dyslexia are lucky in a way, because they are identified. There are many other children out there who are not identified and who have just been disconnected.

We must direct all of our resources and efforts to establish multidisciplinary centers to treat these children. Insurance companies should pay for evaluations, both medical and psychiatric, and treatment.

For over a year, I have been paying for speech therapy for these children. They are able to talk, but they do not know what to do with their mouths. I have had 10-year-olds wake up and talk. Insurance companies do not pay for rehabilitative services for these children. These children are physically ill, immunosuppressed, have a chronic autoimmune disorder affecting multiple organ systems. We must get funding to look at the etiology of autism and identify these children prior to autistic regression and prevent this disorder. Implementing vaccine policies which are safe for all children should be our first priority.

Mothers from all over the country have brought pictures of their autistic children to Washington this weekend. Most of these children were born normal and lost to "autistic regression." Look into their eyes, and you will hear their silence.

Mr. BURTON. Thank you very much. We are going to read the text of your comments very thoroughly.

Dr. MEGSON. Thanks.

Mr. BURTON. Dr. Upledger.

[The prepared statement of Dr. Megson follows:]

Testimony

By

Dr. Mary Megson
Richmond, VA

To

Government Reform Committee

Hearing on

Autism – Present Challenges, Future Needs – Why the Increased Rates?

04/04/00

Mr. Chairman, Honorable Dan Burton and members of the committee;

My name is Mary Norfleet Megson. I am a board-certified pediatrician, Fellowship trained in Child Development, a member of the American Academy of Pediatrics and Assistant Professor of Pediatrics at Medical College of Virginia. I have practiced pediatrics for twenty-two years, the last fifteen years seeing only children with Developmental Disabilities, which include learning disabilities, attention deficit hyperactivity disorder, cerebral palsy, mental retardation and autism.

In 1978, I learned as a resident at Boston Floating Hospital that the incidence of autism was one in 10,000 children. Over the last ten years I have watched the incidence of autism skyrocket to 1/300-1/600 children.[1] Over the last nine months, I have treated over 1,200 children in my office. Ninety percent of these children are autistic and from the Richmond area alone. The State Department of Education reports that there are only 1522 autistic students in the state of Virginia.

MHMR agencies have created local infant intervention programs, and have had a hard time keeping up with the numbers of delayed infants and toddlers. I have served as advisor to the City of Richmond and the surrounding counties have established entire programs for autistic children that fill multiple classes in several schools in each district. The segment of children with "regressive autism," the form where children develop normally for a period of time then lose skills and sink into autism most commonly at 18-24 months of age, is increasing at a phenomenal rate. I am seeing multiple children in the same family affected, including in the last week four cases of "autistic regression" developing in four year old children after their MMR and DPT vaccination. In the past, this was unheard of.

In the vast majority of these cases, one parent reports night blindness[2] or other rarer disorders which are caused by a genetic defect in a G protein,[3] where they join cell membrane receptors, which are activated by retinoids, neurotransmitters, hormones, secretin and other protein messengers. G proteins are cellular proteins that upgrade or downgrade signals in sensory organs that regulate touch, taste, smell, hearing and vision. They are found all over the body, in high concentration in the gut and the brain:[4] and turn on or off multiple metabolic pathways including those for glucose, lipid, protein metabolism[5] and cell growth and survival.[6] Close to the age of "autistic regression," we add pertussis toxin, which completely disrupts G Alpha signals.[7] The opposite G proteins are on without inhibition leading to:[5]

1. Glycogen breakdown or gluconeogenesis. Many of these children have elevated blood sugars. There is sixty-eight percent incidence of diabetes in parents and grandparents of these children.

2. Lipid breakdown which increases blood fats that lead to hyperlipidemia. One third of families has either parent or grandparent who died from myocardial infarction at less than 55 years of age and diagnosed with hyperlipidemia.

3. Cell growth differentiation and survival which leads to uncontrolled cell growth. There are 62 cases of malignancies associated with ras-oncogene in 60 families of these autistic children.[9] The measles antibody cross reacts with intermediate filaments which are the glue that hold cells together in the gut wall. The loss of cell to cell connection interrupts aproptosis or the ability of neighborhood cells to kill off abnormal cells. The MMR vaccine at 15 months preceeds the DPT at 18 months which turns on uncontrolled cell growth differentiation and survival.

One-third of families report colon cancer in the parents or grandparents.[10] The genetic defect, found in 30-50% of adult cancers, is a cancer gene (ras-oncogene). It is the same defect as that for congenital stationary night blindness.[11]

G protein defects cause severe loss of rod function in most autistic children.[12] They lose night vision, and light to dark shading on objects in the daylight. They sink into a "magic eye puzzle," seeing only color and shape in all of their visual field, except for a "box" in the middle, the only place they get impression of the three dimensional nature of objects. Only when they look at television or a computer do they predictably hear the right language for what they see. They try to make sense of the world around them by lining up toys, sorting by color. They have to "see" objects by adding boxes together, thus "thinking in pictures." Their avoidance of eye contact is an attempt to get light to land off center in the retina where they have some rod function. Suddenly mothers touch feels like sandpaper on their skin. Common sounds become like nails scraped on a blackboard. We think they cannot abstract, but we are sinking these children into an abstract painting at 18 months of age and they are left trying to figure out if the language they are hearing is connected to what they are looking at, at the same time.

The defect for congenital stationary night blindness on the short arm of the X chromosome affects cell membrane calcium channels[13] which, if not functioning, block NMDA/glutamate receptors in the hippocampus,[14] where pathways connect the left and right brain with the frontal lobe. Margaret Bauman has described a lack of cell growth and differentiation in the hippocampus seen on autopsy in autistic children.[15] The frontal lobe is the seat of executive function, attention, inhibition of impulse, social judgement and all executive functions.

When stimulated, these NMDA receptors through G proteins stimulate nuclear Vitamin A receptors discovered by Ron Evans, et al Dec 1998.[16] When blocked, in the animal model, mice are unable to learn and remember changes in their environment, they act as if they have significant visual perceptual problems, and have spatial learning defecits.[17]

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Of concern the Hepatitis B virus, protein sequence was isolated in the *gene* for similar retinoid receptors (RAR beta),[18] which is the critical receptor important for brain plasticity and retinoid signaling in the hippocampus.[19] After the mercury is removed, I understand we will restart Hepatitis B vaccine at day one of life. Studies need to be don to determine if this plays an additive roll in the marked increase in autism.

I am using natural lipid soluble concentrated cis form of Vitamin A in cod liver oil to bypass blocked G protein pathways but, turn on these central retinoid receptors. In a few days, most of these children regain eye contact and some say their "box" of clear vision grows. After two months on Vitamin A treatment, these children, when given a single dose of bethanechol to stimulate pathways in the parasympathetic system in the gut, focus, laugh, concentrate, show a sense of humor, and talk after 30 minutes as if reconnected.[20]

This improves cognition, but they are still physically ill. When these children get the MMR vaccine, their Vitamin A stores are depleted, they can not compensate for blocked pathways. Lack of Vitamin A which has been called "the anti-infective agent," leaves them immuno-suppressed. They lack cell mediated immunity. T cell activation, important for long term immune memory, requires 14-hydroxy retro-retinol. On cod live oil, the only natural source of 14HRR, the children get well.

I live in a small middle class neighborhood with twenty-three houses. I recently counted thirty children who live in this community who are on medication for ADHD. One week ago, my oldest son who is gifted but dyslexic had twelve neighborhood friends over for dinner. As I looked around the table, all of these children, but one had dilated pupils. After two and one half months of taking vitamin A and D in cod liver oil, my son announced, "I can read now. The letters don't jump around on the page anymore." He is able to focus and his handwriting has improved dramatically. In his high school for college bound dyslexic students, 68 of 70 teenagers report seeing headlights with starbursts, a symptom of cogenital stationary night blindness.

I think we are staring a disaster in the face that has affected thousands of Americans. The children with autism or dyslexia/ADHD are lucky. There are many other children not identified, just disconnected.

We must direct all of our resources and efforts to establish multidisciplinary centers to treat these children. Insurance companies should pay for evaluations, both medical and psychiatric, and treatment. These children are physically ill, immuno-suppressed with a chronic autoimmune disorder affecting multiple organ systems. Funding to look at etiology of autism, to identify children at risk prior to "autistic regression," and to prevent this disorder is imperative. Implementing vaccine policies that are safe for all children should become our first priority.

Mothers from all over the country have brought pictures of their autistic children to Washington this weekend. Most of these children were born normal and lost to "autistic regression." Look into their eyes and you will hear their silence.

Thank you

Mary N. Megson, MD

References

1. Rollins R. A report to the California state legislature 3/1/99, personal communication.

2. Megson M. Is autism a G alpha protein defect reversible with natural vitamin A?. J Med Hypo 2000 Mar.

3. Farvell Z, Bourne H, Iiri T. The expanding spectrum of G protein diseases. N Engl J Med 1999;340:1013.

4. Farvell Z, Bourne H, Iiri, T. The expanding spectrum of G protein diseases. N Engl J Med 1999;340:1012.

5. Meisenberg G, Simmons, W. Principles of Medical Biochemistry. New York: Mosby, 1998:586.

6. Fauci A, Braunwald E, Isselbacher K, et al. Harrison's Principles of Internal Medicine. 14th ed. New York: McGraw-Hill, 1998:505-11.

7. Farvell Z, Bourne H, Iiri T. The expanding spectrum of G protein diseases. N Engl J Med 1999;340:1018.

8. Meisenberg G, Simmons W. Principles of Medical Biochemistry. New York: Mosby, 1998:586.

9. Fauci A, Braunwald E, Isselbacher K, et al. Harrison's Principles of Internal Medicine. 14th ed. New York: McGraw-Hill, 1998:509.

10. Cohen A, Bennett C. Rheumatology and Immunology. 2nd ed. New York: Grune and Stratton, 1986:442.

11. Drujo, TP, Hahn LB, Reboul T, Arnaud B. Missense mutation in the gene encoding the alpha subunit of rod transducin in the naugareit form of congenital stationary night blindness. Nat Genet 1996 July; 13(3):358-60.

12. Realmuto G, Purple R, Knoblock W. Electroretinograms in four autistic probands and six first degree relatives--. Canad J Psy 1989:34:435-9.

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13. Bech-Hansen NT, Naylor MJ, Maybaum TA, et al. Loss of function mutations in a calcium channel alpha 1-subunit gene in Xp11.23 causes incomplete congenital stationary night blindness. Nat Genet 1998;19(3):264-7.

14. Meisenberg G, Simmons W. Principles of Medical Biochemistry. New York: Mosby, 1998:587.

15. Bauman M. The Neurobiology of Autism Spectrum of Developmental Disorders. [Brochure]. XVIII. Baltimore: Johns Hopkins, 1995 1-2.

16. Chiang M, Misner D, Kempermann G. An essential role for retinoid receptors RAR and RXRγ in long term potentiation and depression. Neuron 1998 Dec;21:1351-53.

17. Chiang M, Misner D, Kempermann G. An essential role for retinoid receptors RARβ and RXRγ in long term potentiation and depression. Neuron 1998 Dec;21:1351.

18. Sporn M, Roberts A, Goodman D. The Retinoids. 2nd ed. New York: Raven Press, 1994:339.

19. Sporn M, Roberts A, Goodman D. The Retinoids. 2nd ed. New York: Raven Press, 1994:526.

20. Sporn M, Roberts A, Goodman D. The Retinoids. 2nd ed. New York: Raven Press, 1994:339.

Dr. UPLEDGER. Thank you.

I am John Upledger. I am an osteopathic physician, and I thank you for inviting me to come and present today.

I should probably tell you a little bit about my background first, because you will understand that I am coming at autism not in disagreement with anyone but by adding another parameter to it.

First of all, I used to teach biochemistry, so the molecular things are not new to me. I practiced general medicine and surgery for about 11 years in Clearwater, FL and then got into the rather avant garde things, and they invited me up to Michigan State University, where I became a clinician researcher in the Department of Biomechanics.

Being a researcher in biomechanics, I was researching a system which ultimately became called the craniosacral system. The craniosacral system is simply a semi-closed hydraulic system. The boundary of the hydraulic system is the dural membrane which encases the brain and spinal cord and provides sleeves for all of the cranial nerves and for the spinal nerve roots. The fluid inside it is cerebrospinal fluid, essentially. Of course, there is blood flowing and so on and so forth within vasculature, but it is not really part of the system. And it is called "semi-closed" because the inflow of the volume is controlled, and it is rhythmical, and the outflow is rather constant and reabsorbs the fluid; so you have a circulation of fluid with a rhythmical rise and fall of fluid volume and pressure within the system.

If one looks at advances as we go along, we used to think that cerebrospinal fluid bathed the surface of the brain, and that is what it did. About 8 years ago, it was very definitely shown using radioactive tracers that cerebrospinal fluid is formed in the ventricles of the brain, and within seconds of its formation, it not only bathes the surface but it penetrates all the spaces between all the cells that form the brain; it also goes down the spinal cord internally as well as externally.

More recently, in a symposium called "Neuroprotective Agents" by the New York Academy of Science, I came across a piece that had just been discovered, that is, that cerebrospinal fluid not only circulates nutrients and carries away waste products, but it also has chelating agents in it, so it cleanses the brain of metallic deposits, which would be the mercury, the aluminum and that kind of thing.

So it is very important, and if you look at it this way, it is extremely important, that cerebrospinal fluid flow be kept moving. Stagnation of cerebrospinal fluid is going to lead to brain dysfunction.

In my work at Michigan State in developing this department, developing this whole system, what happened was that it was decided that I would be working with brain-dysfunctioning children to see the applications. Autism happened to be one of the things that I was assigned to, so for 3 years, I spent 2 days a week at the Genessee County Center for Autism, and I went in there not even understanding the first thing about what autism was.

We did work with what was called hyperkinesis in those days, and we found out on a structural level that the hyperkinetic child could be relieved of his hyperkinetic activity if we released a compression at the base of his skull between the first cervical vertebra and the occiputal base. Tracing this backward, this happens a lot during delivery. The baby is face down, the obstetrician assists the baby coming out under the pubic bone, the head comes base or forward, and the cervical vertebra goes that way, and they jam together. You release that jamming, and you get rid of your hyperkinesis in a matter of minutes many times.

That is not the only cause for hyperkinesis, but when it is there, and you release it, it is very definitely going to show you clinically that it is over.

We also found out that in newborns we could treat colic this way.

When I got into looking at autistic behaviors, there were several things that we noticed, and being a novice, I was not about to accept anybody's word for anything. I went over there with a neurophysiologist and another fellow who was a generalist in science, a design specialist, and we started going every week, Thursday and Friday.

Our observations showed first of all that a lot of the kids were banging their heads. There were 28 kids in that first year we went there. I noticed their head-banging, and they were chewing on their wrists; they would get all the way down to the tendons sometimes. We were also told they sucked on their thumbs, and I saw that, but they were not making an airtight things with their lips; what they were really doing was pushing up on the base of their skulls.

So we thought about this a lot, and one would say, OK, they are banging their heads, and this happened at a behavior modification center that we were working at, so I had them take the helmets off, and we let them bang their heads and watched very carefully, and it looked like they were trying to knock something loose in their heads, as if something was jammed together.

When we started looking at their wrists and everything, I thought, OK, maybe they are inducing a controlled pain for a pain they have in their head that is uncontrolled, because I think anybody here would agree that sometimes when something hurts, and you just cannot get to it, you will give yourself a pain somewhere else, and it at least gives you some sense of comfort. And the other thing that might be happening is when they are chewing, they are inducing endorphin production and getting that natural analgesia, because endorphins are like a natural morphine.

The thumb-sucking clearly, to the point where it was causing the teeth to protrude forward over a period of time, the thumb-sucking clearly was an attempt to mobilize the base of their skull.

Anatomically—and now I am in biomechanics, so I am thinking anatomically, and what I am doing a lot of on the other days off is getting very fresh cadavers, dissecting them, studying membranes and all of that kind of thing on the inside of the head, so I am tying these two things together. So we began to get the idea that the cranial rhythm or the movement inside that head was not giving the amplitude that we were looking for in other children. The autistic head just did not have the craniosacral rhythm, the activity, so it was not pumping cerebrospinal fluid.

Hence, you would get an accumulation of toxic metals. You would also get a deficit in the delivery of fluid carrying nutritional agents and carrying away metabolic byproducts. You would also get a thing that we began to understand clearly, and this became the model we put forth after about the second year, and that is that something occurred to denature the membrane biochemically so that it would not expand and accommodate the normal growth pattern of the skull as it was trying to expand in the brain and trying to grow. If the brain is trying to grow against the resistance of a membrane that is having difficulty expanding, you are going to cut down cerebrospinal fluid exchange and you are going to cut down blood flow.

We finally got into it and started decompressing heads forward to backward in this direction—forehead forward, back of the head backward. We would just sit there and hold it, a small force over a long period of time, and ultimately, the head would begin to expand in that direction. When it did, those things that looked like they were trying to create their own pain—the thumb-sucking stopped, the head-banging stopped, and the wrist-chewing and that kind of thing stopped—they stopped spontaneously after we released that particular forward-to-backward compression.

That was probably very close to 100 percent response. Now, you had to spend a lot of time to get an autistic kid to lie on a table in an autistic center and let you work on them and have them be quiet, but after we saw them three or four times, they would actually come in, lie down on the table, take your hands and place them on their head where they wanted them. And I would go along with that.

The next thing I wanted to do was expand the head side-to-side. I had a lot of graduate students with me all the time and did not know what to do with them, so I would put one student on each leg and one student on each arm, and I would just start expanding the head laterally. Well, we found out that after we got that expansion done laterally, first of all, the child would very, very much relax, and the body would go into all kinds of contorted positions and stay there. As they stayed in that contorted position, you could feel energetic changes going on throughout their body, and when they finished that particular thing, they were very liable to turn around and kiss you and give you a hug. And after that, they became sociable.

So what I am looking at is a model here that says, OK, decompress these membranes. What caused the membranes not to expand? And then, historically, we started looking at it. Febrile episodes were extremely common. The fever could be due to a vaccine reaction, it could be due to a viral infection, it could be something in utero that occurred when Mom had a little fever when she was still pregnant. And it seemed as though it was taking about 2 to 3 weeks historically for most parents to discover the signs of the changes occurring which were later called "autism"—after the febrile episode.

So we chalked up the idea that most likely febrile episodes could cause a change in the biochemistry of the membrane so that it did not accommodate the growth process as readily as it could. Now, that does not fly in the face of genes at all, because I am sure that genes control some of the accommodative process of the dural membrane, and therefore, if they have a genetic predisposition to a membrane that is vulnerable, it takes a smaller shock to make the membrane become less accommodative. That does not bother me at all.

We also found—after I got this going, I was invited to London to start an autistic treatment program for children in a craniosacral therapy clinic, and again, in Brussels. And in London, I have to tell you that I wound up evaluating children that I thought were autistic from a craniosacral evaluation perspective—I wound up with 42 children in that clinic, and I was there for about 4 days evaluating them—and 38 of the parents out of the 42 said the febrile episodes were subsequent to a vaccine. And most incriminating—and this would be in the late seventies—the vaccine most incriminated by the parents in their opinion was pertussis.

When I went to Brussels, it was an entirely different thing. The feel of the head, the energy patterns in the head, everything was different. Almost all of the autistic kids I picked up there had been delivered by vacuum extraction—that is where they put the suction cup on the head and just pull. If you consider a plumber's tool, and you clamp it on the top of the head and pull, what you are going to do is extravasate a lot of capillary blood, and when blood breaks down and deteriorates, it becomes bile in one of its stages, which is extremely irritating, so the tissue that has these red blood cells that are deteriorating begins to contract and cause scarring and lose its accommodative ability. In Belgium, that was the main cause we came across.

In this country, there is a great variation. At the autistic center where I spent the first 3 years of my experience, I would have to say that two-thirds of those kids were in foster homes, so we did not know much about their backgrounds. But when I finished the contract for autism at the Genessee County Center in Flint, we opened a clinic at the university, and there, I have to say that probably 50 percent of the parents were totally convinced that the autism was secondary to a febrile episode which more often than not, they related to a vaccine reaction. And I do not say that that is yes or no, but I say it certainly does deserve a healthy look.

Some of the things that I would like to share with you that we did—and it is interesting that Dr. Megson talked about parasympathetic, because one of the pieces of research we did on our autistic children was to monitor with a thermograph the hand as we were stretching the membranes in the head. And as we got some releases, the temperature of the hand would go up 2 or 3 degrees Fahrenheit, which indicates that the blood vessels in the hand are relaxing; you are getting better blood flow. And in order to get better blood flow, you have to reduce the activity level of the sympathetic nervous system which she was referring to, and that is the flight-or-fight system.

So we were able to reduce their sympathetic activity by working on their head and stretching their membranes.

Now, the whole thing begins to make a lot of sense if you consider, then, the things that we were watching happen. If we got a child's membrane stretched in all directions, and he was feeling pretty good, he would take on a lot of good behaviors; and if we got that to happen and then—our research was always held up from June until September when school was out, getting the contract renewed and all that kind of thing, so we had a lot of children who did not receive treatment for 2 or 3 months, and they would regress. I look at it this way—their head is trying to grow, and their brain is trying to grow, but they need a mechanical stretching activity which is craniosacral work to keep the membrane spreading enough so that it will accommodate that intended growth process. And if you do not have that for a while, then you begin to regress because the pressure on the brain and the reduction of fluid activity, the reduction of blood flow, all begin to recur.

So the next thing we try to do—and we have done this successfully I would say with 30 percent or so of our parent groups, and I did not have the opportunity to do it the way I would really like to—but we taught them to do this treatment process once a week and maybe see a therapist every 6 weeks or so. That seemed to work if the parents were willing and able to learn how to do it. It is not hard once you get the initial job done; then it is a question of maintenance, which is not too difficult. And that is one of the things we look for.

I left the university in 1983 and took time out to develop a prototype for a holistic health center for Unity Churches, and then we started our own institute in 1985, at the end of 1985. Since that time, the way we handle the problems is, first of all, we do not always focus on autism, because the kind of difficulties we have with the craniosacral system can involve anything from autism to hyperkinesis to chronic pain—seizure activity is a big one we work with—and all those kinds of things, but about four times a year, we will have a special intensive program for just autistic children. That is what we do, and we try to help the parents learn how to work with it. And when I say "intensive," it is a week, and it is from 10 a.m., until 6 p.m., and it is hands-on work almost all the time. During that week, we get things pretty well taken care of. And I do not think we have had a child yet who did not show at least 50 percent improvement during that period of time, and most of them do significantly better than that.

That is about where I am.

Mr. BURTON. Very good. That was a very good lecture. I enjoyed that, and we will have some questions about whether or not any of our health agencies have picked up on your procedures.

Dr. UPLEDGER. Thank you.

Mr. BURTON. Dr. Pratt.

[The prepared statement of Dr. Upledger follows:]

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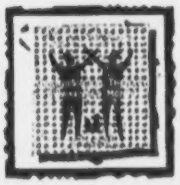

Autism – Observations, Experiences and Concepts

John E. Upledger, D.O., O.M.M.

An Etiologic Model for Autism

The following model was first formulated based upon hands-on experience with autistic children, historical information gained from their parents, observations of the children's behaviors, their responses to treatments, and our laboratory results.

During the normal, physical growth period of the child's brain and cranium, it is necessary that the meningeal membranes that line the cranial vault and cover the surface of the brain grow and expand in synchrony with the growth of these structures in order to accommodate the natural maturation process. For some reason the meningeal membranes, especially the dura mater, lose their accommodative growth abilities, thereby disrupting the normal expansion of brain and cranial vault. This loss of accommodative quality of the dura mater is most likely due to biochemical changes in its make-up. These biochemical changes may be the result of febrile stressor episodes for any reason, such as viral infections, vaccine reactions and so on.

The manual stretching of the restrictive dura mater by the use of CranioSacral Therapy techniques has provided impressive improvement in autism. The therapy must be continued until the child has reached full growth, because once the dura mater has lost its accommodative ability, it must be physically stretched by a therapist. CranioSacral Therapy accomplishes this task non-invasively by using the various related bones to which the dura mater attaches as handles to stretch the membranes.

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Background

In the fall of 1976, as a clinician-researcher at Michigan State University (MSU), I began a study of autism at the Genessee County Center for Autistic Children in Flint, Michigan. My co-investigators included Ernest Retzlaff, Ph.D. in neurophysiology, Jon Vredevoogd, M.F.A. associate professor of design at MSU, and a wide array of graduate students in the MSU colleges of osteopathic and allopathic medicine, as well as a few in the department of psychology. Our research project lasted three school years (September – June). We worked onsite two days per week during these school years. The center for autism was a day school and it was closed during the summer. We consistently averaged 28 to 30 autistic children in our program. About two-thirds of these children were in this study for at least two of the three years.

The grant support for the study was awarded on an annual basis. It is my understanding that the monies originated from NIMH and were funneled to me as principal investigator via the state of Michigan and Genessee County. The funding ended at the end of the third year quite abruptly. My understanding at that time was that the state chose to put the monies into other more pressing projects. I was told by the Genessee County officials that autism was not the highest priority and that the tax base in the state was not very stable.

During these three years and subsequently, I saw private patients diagnosed as autistic coming from a variety of sources. These children were seen at the university clinic.

After leaving MSU in 1983 I moved to Florida where, in 1985, we founded The Upledger Institute. During the interim, 1983 to 1985, I developed a prototype wholistic healthcare center for Unity Church of Palm Beach. During this period with Unity Church I treated only a few autistic children. Shortly after The Upledger Institute was begun we developed a one-week intensive treatment program for autistic children, which is still in operation. It is offered three or four times each year for only autistic children. The program is a five-day week, with approximately six hours per day of hands-on treatment. Parents are included and offered training in the treatment and management of their autistic children.

Since the beginning of my work with autistic children, CranioSacral Therapy has been the main therapeutic focus, coupled with nutritional supplements as they seem indicated.

Observations

Since my first experiences with autistic children I have made several observations that have been consistent and have influenced my concepts of etiology and therapeutic management.

These observations are as follows:

1. Historically, the onset of autistic behaviors is often preceded by some sort of febrile episode. This febrile episode occurs most often about two weeks prior to the parent noticing behavioral changes. However, the time between the fever and the onset of noticed symptoms may vary from a few days up to a few months. Certainly, the length of time reported is dependent upon the powers of observation by the parents, their level of denial and so on. The fever could be resultant to viral infection, a vaccine reaction or any other cause. Our historical information comes from parents interviewed by me personally in the US, Canada, England and Belgium. In all of these places I took histories from parents. I also evaluated the children from a craniosacral system perspective.

2. Some of the behaviors observed in autistic children are attempts to change/correct physiological and/or anatomical dysfunctions that may be causing pain or discomfort. Many autistic children are known to bang their heads, chew on their wrists and/or the bases of their thumbs until deep tissue (tendon sheath) is visible, and/or they may suck on their thumbs so vigorously that the front upper teeth begin to displace forward. Actually, these thumb-sucking children are pressing on the roof of the mouth as hard as they can.

We have observed that, when specific corrections of the craniosacral system are successfully carried out, these behaviors spontaneously cease. It is my opinion that the head-banging child is trying to

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release a compressive force in the head that is quite painful. When we release this compression, head banging stops. This compression is from the front to the back of the head.

Regarding the chewing on the wrist and thumb base, there are three theoretical possibilities that may be valid. First, this self-mutilating activity may be a substitution of a controlled pain that overrides and is more acceptable than a head pain that is not controllable. Second, the self-mutilation may also serve to stimulate the synthesis and release of the natural pain relievers (endorphins) that are nature's way of offering relief from pain biochemically. Also, there is a gate theory of pain developed by Melzack and Wall that suggests that, when the quantity of pain impulses coming into the brain exceeds an upper threshold, all impulses are blocked from entry into pain-perception centers in the brain. The autistic child may have found that when he/she inflicts more and more injury/pain upon himself/herself, the pain is no longer present.

I have seen consistently that, when we are able to release reactions of the membranous lining of the floor of the cranial vault in a front to back direction, these "autistic" behaviors (listed above) disappear "spontaneously."

3. It was consistently observed that CranioSacral Therapy directed at alleviation of abnormal transverse (side to side) compression of the cranial vault resulted in the child immediately demonstrating love and affection. The child will often hug and kiss the therapist after the compression has been released. Subsequently, improved socialization is often demonstrated by showing love and affection to parents and caretakers, as well as beginning to interact with other children and adults, whereas previously their interactions were with inanimate objects. Additionally, during the CranioSacral Therapy session the child often releases a lot of emotion.

4. Thermographic monitoring of the autistic child's hand during successful but basic CranioSacral Therapy sessions demonstrates hand warming, often as much as 2 to 3 degrees Farenheit. This offers evidence of increased blood flow to the hand resultant to the CranioSacral Therapy that is applied to the head. The increased blood flow is necessarily related to relaxation of

the autonomic (sympathetic) nerve control of the blood vessels. This sympathetic nervous system relaxation results in a reduction of internal physiological and emotional stress factors.

5. It has been noted that most autistic children are very shallow breathers. While working at the Genessee County Center for Autism, I had the children breath 10% carbon dioxide in 90% oxygen for about five minutes in the morning, five days per week. This seemed to enhance the breathing activity for an extended period of time after the five-minute session was completed.

6. Hair analysis for toxic minerals was done on all children in the Genessee County study. We could see no consistent patterns of abnormality in mineral levels in the hair of the children.

7. Extensive blood analysis was done on all children in the Genessee County study. This analysis included standard blood-cell counts, routine blood-chemistry studies, isoenzyme studies, and protein electrophoresis studies. No consistent patterns of abnormality were seen.

8. Ultimately, all of our examinations consistently revealed that the intracranial membranes were very tight. Our findings suggested that for some reason the meningeal intracranial membranes, especially the dura mater that is very tough and waterproof, were not expanding along with the normal growth of the skull bones and the brain. I tested this concept by examining 63 children who had been rated as either autistic or childhood schizophrenic by Dr. Bernard Rimland who directed the Child Behavioral Research Center in San Diego. I had seen none of these children, nor their records, previously. I was able to pick out the autistic children from the sample with over 90% accuracy simply by manually evaluating each child's craniosacral system.

9. Favorable responses to CranioSacral Therapy were often lost when there was no treatment for three or four months. This suggests the lack of growth of the dura mater while the skull and brain grow as a contributing cause for autism.

Suggested Conclusions

The aforementioned observations, coupled with the observed clinical responses to CranioSacral Therapy, suggest that compromise of the accommodative quality of the intracranial meningeal system, especially the dura mater, to growth of the skull and brain is at the very least a large contributor to the problems of the autistic child. The dura mater can be stretched by the use of CranioSacral manual techniques applied to the external surface of the cranium. This work affords some relief from the membranous restriction imposed upon brain and skull bones. The treatment must be continued regularly because the accommodative enlargement of the membrane compartment is quickly used up as the child and his/her brain and skull continue to grow.

The Treatment

The treatment that I suggest is regular CranioSacral Therapy until the child is fully grown. This treatment is best administered on a weekly basis. However, it can be administered at longer intervals if close watch is kept for signs of regression. When these signs do appear, treatment should be resumed. If signs of regression appear, it may take up to five or ten sessions to re-establish the accommodations for brain and skull growth by the dura mater membrane. On a weekly basis, one treatment is usually enough to maintain favorable growth conditions.

It is also suggested that nutritional supplements be given in order to ensure the restoration of vitality of a brain that has been compressed for a significant amount of time. Among the suggested nutrients are B complex, B12, docosahexaenoic acid (Neuromins), alpha lipoic acid, and a good multivitamin and mineral preparation.

We have had some success in teaching parents to treat their autistic children using CranioSacral Therapy. This offers them some degree of independence from geographical location requirements near CranioSacral Therapists. If the child shows reasonable progress using parental treatment, we suggest re-evaluation by a skilled CranioSacral Therapist about every six months.

Ms. PRATT. Mr. Chairman, thank you for the opportunity to present testimony today concerning autism treatment options and research. I am here today kind of in multiple roles, first as director of the Indiana Resource Center for Autism, located at Indiana University's Indiana Institute on Disability and Community, and as a board member of the Autism Society of America.

I would like to commend you and thank you for holding this hearing. I think that for too many years, the voices of some of the children you see on the posters have not been heard; this gives them a wonderful opportunity to be heard.

While I have your attention, I would encourage you to do two things. One is to continue funding the Centers for Disease Prevention and Control in terms of looking at the incidence and prevalence of autism. As I was working with your office on providing testimony for today, it is clear that we do not have a true idea of the incidence and prevalence of autism across the United States.

The other thing that I would encourage you to do is to work with your colleagues on supporting H.R. 3301, which is the omnibus children's health bill, which would provide clear direction to the CDC and the National Institutes of Health.

I am probably the oddity on this panel. I am not a physician. I spend a lot of time in classrooms and in homes and around the State of Indiana, visiting children and their families and their educators and other professionals who support them. And while I know that there is broad disagreement about whether there really is an increasing incidence of autism, I know that we are incredibly busy. I know that I hear from professionals out in the field and from family members that they truly are seeing many more children than they ever saw in the past. So I have to listen to their words.

In terms of the potential causes of autism, I hope you realize that autism is referred to as a "spectrum disorder," and along with that, that probably reflects the idea that there is a spectrum of reasons why children do develop the characteristics associated with autism and that each of the professionals and family members who are here today are painting just a piece of that picture for you. I would really encourage you to propose legislation and funding that will look at the possible multiple causes of autism, and along with the vaccination issue, the issues around environmental situations and other issues which parents keep reporting as being possibly related to the occurrence of autism.

I have never heard from any of the families an issue about whether they want to vaccinate their children or not. I think the issue is in terms of safe vaccinations. As a professional in the State of Indiana, I know there is broad disagreement about whether there is a link between autism and vaccinations.

As a professional who works with families every day, here is my position. If I could have helped those four families who are here today to avoid having a child diagnosed with autism by giving them accurate information, I would have done so in a heartbeat regardless of what the research tells us. I think that is the issue that all of us face, that when the research may not be proving it, when we hear the stories, we want to avoid further stories being told.

In addition to looking at the research behind causes, I would also encourage us not to forget about the 500,000 other individuals and their families who currently have a diagnosis of autism and the needs that they have. The families and several of the panelists today have talked about some of those needs.

The first one is in terms of early intervention. I really applaud the National Academy of Sciences and the National Institutes of Health for starting to look at the essential components of early intervention programs that are most effective. I think we have focused a lot of effort on looking at specific programs, and while there is some broad disagreement about which of those specific programs is most effective, I think there is some general agreement arising about the components of those programs, and I hope that those things will really be looked at.

Based on the testimony that I have heard during the National Academy of Sciences meetings, it is very clear that additional research is needed to try to really build a case for the various components of effective programming.

The next issue that I would like to cover is full funding for IDEA and the professional development efforts. In a recent report, it was noted that 44 out of 50 States are not in compliance with the "free and appropriate education" mandate of the Individuals with Disabilities Education Act. While those reasons may differ from State to State, I believe part of the reason is due to funding.

In addition to that, there is a tremendous need for trained professionals in the field. Sometimes, professionals are placed in the role of supporting challenging individuals, and they do not receive any training or guidance or assistance in being able to do so. So I would really encourage that we look at providing funding support to States for continued professional development.

In addition to that, you have heard from many of the parents about the need for accurate information to pediatricians and other physicians who play a critical role. They are oftentimes the first people that parents talk to when they think their children may have a diagnosis of autism. The information that they can provide to families can help to set them on either the right track or the wrong track. So I really encourage education for them.

Another issue that I hear a lot from families is in terms of insurance coverage and funding sources. In my written testimony, I provide the example of a family in Indiana that was denied coverage for their child's appendectomy because he had a diagnosis of autism. Autism is considered a pre-existing condition by some insurance companies, so these children are excluded from insurance coverage.

I hope you realize the tremendous accommodations that the families that you saw today have had to make to be here today, and in their lives on a daily basis. The tremendous financial devastation that many of them face, the stresses on their marriages—and I am so glad to see that many of them are here, fathers and mothers together—the stress on their entire lives is just unbelievable. You know first-hand as a grandparent how tremendous the stress can be.

I also need to tell you that your support is greatly appreciated by the autism community. Your support is even more greatly appreciated by your daughter today.

I also hope you realize that when insurance companies turn families away, they look to other funding sources, whether State or local agencies, and in many cases, that money, that funding, is nonexistent or is inadequate for the family support needs. Families are told that they have a window of opportunity for their children, and at that point, they have run to get those services and supports that they need; and when they are denied the funding they need to be able to provide those services, they will do anything and risk tremendous devastation to be able to reach those goals.

A population that I hope we will not forget is the adults who have autism. We have a high percentage of individuals who remain unemployed, who are very competent, talented individuals with autism; others who are underemployed or in jobs which really do not match their talents and skills and interests.

In addition, many of them choose living options that are only a far-off dream—to live in a community, to have access to the same rights and privileges as every other citizen of the United States. While progress has been made in this area, much is still left to do.

While I commend the committee for taking this opportunity to listen to families today, I also urge you to support authorizing legislation and appropriation provisions that will further the state of autism research. While much progress has been made, remember that there is still much to do.

Thank you.

Mr. BURTON. Thank you very much, Dr. Pratt.

Dr. Hirtz.

[The prepared statement of Ms. Pratt follows:]

Prepared Testimony
Before the
House Committee on Government Reform

April 6, 2000

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Mr. Chairman, Thank you for the opportunity to present testimony concerning Autism Treatment Options and Research. I am here today as director of the Indiana Resource Center for Autism located at Indiana University's Indiana Institute on Disability and Community and as a member of the Board of Directors of the Autism Society of America.

I would like to begin by commending this Committee for directing its energies toward today's hearings. For too long, individuals with autism spectrum disorders have not had their voices heard. While I have the attention of the Members of the Committee, let me urge you to do two things that will help. First, please send a letter to your colleagues at the Appropriations Subcommittee that funds the Centers for Disease Prevention and Control (CDC). Ask them to provide the proposed funding to expand the CDC's work in gathering national data on the prevalence of autism. Second, join 41 of your Colleagues in co-sponsoring H.R. 3301, an omnibus children's health bill that provides clear direction to the CDC and the National Institutes of Health for speeding up the research and public education in autism.

The increasing incidence of autism has generated a renewed and much needed focus on autism spectrum disorders. As the incidence increases, research into both the causes and effective treatment options becomes paramount. Across the United States, families are struggling with the many challenges presented by a family member with autism and the systems which are needed to support him/her. Below are a few comments which reflect major issues often heard. These major issues include, research into potential causes, early intervention, insurance coverage/funding mechanisms, adult options, and trained professionals,

Research into Potential Causes. Autism is referred to as a spectrum disorder to highlight the differences among a population who share a common diagnostic label. Just as these individuals differ in their characteristics, so may they differ in the causes of their autism. It seems clear that autism is a genetic disorder. Children are born with a genetic predisposition for developing the characteristics of autism. At some point prior to, during or after the birth process, something occurs that triggers autism to occur. Potential triggers include environmental factors, illness, complications during the birth process, or factors related to diminished immune systems. One of the triggers that is being considered and discussed by families is the measles-mumps-rubella (MMR) vaccination. While this is not a statement in support of eliminating vaccinations, it is a plea for examining this potential relationship and for developing ways in which to more safely vaccinate children. The hope in examining potential causes is two-fold. First, the idea is that if the cause can be found, a cure will soon follow. While finding a cure may be in the distant future, research into potential causes can have a more immediate impact. If causes are found, such as the MMR vaccination, that can be dealt with immediately, we may be able to prevent numerous families and children from being affected by autism. However, I encourage the committee to support research which will look broadly at potential causes.

At the same, time, I would like to speak to the federal framework of support for those 500,000 individuals currently diagnosed with autism spectrum disorders and their families. These individuals and their families can benefit dramatically from early intervention, special education, and adult services. Yet, there are many barriers to their ability to secure such supports.

Early Intervention. The National Academies of Science and the National Institute on Health are to be applauded for their efforts in examining the status of research related to educating young children with autism spectrum disorders. While there is generally professional agreement regarding essential features of intervention for children with autism spectrum disorders, there is less agreement regarding the "best" specific program. The hope is to be able to identify treatment approaches which will have the greatest long term impact and which are responsive to the core deficits of autism spectrum disorders. Based on testimony provided by leading professionals to the National Academies of Science, it is clear that additional research is needed to determine critical features of programs.

Full Funding for IDEA and Professional Development Efforts. In a recent report, it was noted that 44 out of 50 states are not in compliance with the "free and appropriate education" mandate of the Individuals with Disabilities Education Act (IDEA). While the reasons for this situation may differ in each state, we do know that states need financial support when mandated to provide services.

While IDEA authorizes funding for personnel development, the funding allocated is not sufficient to meet the need. As the incidence of autism grows, we are encountering a stark gap between the demand for trained personnel and the availability of teachers and medical professionals who have had training in how to identify and respond to individuals with autism. In some cases, professionals with little or no training are taking primary responsibility for the education of children who challenge the most trained professional. Across the country, families cry out for training of pediatricians and other medical personnel. Physicians are often the first source of information for families whose children are newly diagnosed. They have a tremendous responsibility for starting parents on the right track. In order to do so, physicians must have more and better information related to diagnosis and treatment.

Insurance Coverage/Funding Sources. When faced with the high cost of interventions, therapies, medications and other necessary support services, families look to state and local agencies for financial resources, and/or to their insurance companies. Often times individuals with autism spectrum disorders are not eligible for insurance coverage. For example, one individual was ineligible for insurance coverage for an appendectomy because autism was considered a pre-existing condition. In other words, even though a physical illness is completely unrelated to autism or its behavioral manifestations, sometimes individuals with autism are denied coverage. This policy is based on a very distorted understanding of what autism spectrum disorders are and how they affect a person's physical health. When faced with the high costs of medical care, therapies, medications, and other treatment approaches and interventions, many find themselves mortgaging their homes to ensure that their child has the best possible care. The financial and emotional toll on the entire family is enormous. Families then turn to other state and local agencies for financial support. These resources are scarce, and in some states non-existent. Families are told that they have a window of opportunity in which to intervene with their child. When resources and services are not available during this critical time period, families are willing to risk financial devastation. The end result is tremendous stress on their marriages, and intense levels of personal stress in coping with their child's autism. And again, this impact is felt by the entire family, including siblings and grandparents.

Employment and Supported Living. Today, a high percentage of individuals across the autism spectrum remain unemployed. When employed, they are often either under employed or in jobs which do not match their talents. Some of our most talented individuals face a life of poverty. For others, living options which allow them to reside in their community and receive needed support is only a dream. While progress has been made in this arena, much is still left to do.

Conclusion

While I commend the Committee for taking this opportunity to listen to families today, I also urge you to support authorizing legislation and appropriations provisions that would further the state of autism research. Support Congressional efforts to fully fund IDEA, providing the supports and services that students with autism need, including adequate training for education personnel. We need better training for medical professionals, more opportunities for employment and supported living, and access to health care coverage. While much progress has been made, there is still much to do.

Dr. HIRTZ. Mr. Chairman, I am Deborah Hirtz of the National Institute of Neurological Disorders and Stroke [NINDS], at the National Institutes of Health.

I have been asked to appear before you today to give the committee and the families of autistic individuals who are here a sense of what we have learned from research, what we hope to achieve, and I want to explain that we at the NIH share the sense of urgency that autistic individuals and their families and advocates feel with regard to unlocking the mysteries of this devastating disorder.

As a physician who takes care of children with neurological disorders including autism, this urgency has a particular intensity for me as well. By presenting information about a broad array of NIH autism research activities, I will try to convey to you the strong commitment of the NIH to increasing our knowledge about autism, what causes it, how best to diagnose and treat it, and we hope not too far in the future, perhaps even how to prevent it.

I would also like to tell you that over the last 5 years, the total NIH funding for autism research has nearly quadrupled. It was $10.5 million in fiscal year 1995 and $40 million in fiscal year 1999.

We now know that autism is much more common than we previously thought. Estimates vary widely, but recent studies suggest that as many as 1 in 500 people may be affected by some form of autism. Recent reports suggest that the number of children with autism may be increasing substantially. It is not clear whether the reported increases can be accounted for by improved or expanded diagnosis, or by the increasing availability of services for autism and it would be necessary to study the trends of that prevalence over time.

The NIH recognizes the pressing need to look into these issues and to do this work and is actively working to design studies that can give us knowledge in these areas. Accurate and consistent diagnosis of autism is one of these difficult areas. To address this problem and in response to the requests of concerned parents, the NIH sponsored a 1998 meeting of major medical and professional societies, parent advocacy groups and Federal agencies to review existing evidence for autism screening and diagnosis. Based on the assembled research and evidence, a consensus statement is near completion as a practice parameter, which is a professional guideline for recommended procedures, criteria and timing for screening and diagnosis in autism. This will be the first time that such a multidisciplinary group has reached consensus on screening and diagnostic procedures in the area of autism. The specific practice parameters or clinical recommendations, once approved, which we expect to be shortly, by the boards of various relevant professional societies, will be published in widely read medical journals.

In the vast majority of cases, no specific underlying cause of autism can be identified. A variety of genetic, metabolic, infectious and unknown factors may be important. The NIH supports research directed at exploring the possible role of these various factors and is exploring the feasibility of a very large, multi-agency, prospective study that could shed light on some of these questions.

A working group convened by NIH in 1995 reached a consensus that for at least a significant subgroup of people with autism, there appears to be a genetic susceptibility that most likely involves multiple genes, and the NIH has conducted two major meetings on the genetics of autism.

An exciting development this past year has been the identification of the gene for Rett syndrome, an autism spectrum disorder. In addition, genetic "hot spots," potential chromosomal locations, for more classic forms of autism have been identified. In another area, NIH is supporting a major pediatric brain imaging initiative to learn how the brain develops in normal infants, children and adolescents. This will provide important data for comparison in studies of developmental disorders such as autism.

Although there is currently no known cure or treatment which can reverse all the symptoms of autism, interventions designed to alleviate specific symptoms are available. In November 1999, the NIH held a workshop in conjunction with the Department of Education on treatments for people with autism and other pervasive developmental disorders. The purpose of this workshop was to evaluate the current biological, behavioral, psychopharmacological and biomedical treatments in autism and to identify critical research needs in autism treatment. The written reports and recommendations from the working groups at this meeting have recently been assembled and are currently being reviewed by the members of the NIH Autism Coordinating Committee, which is a group from various institutes involved that coordinates the NIH research activities, and also by the representatives of autism advocacy groups to see where we go from here in pursuing various avenues of treatment research.

I have just very briefly described some of the NIH autism research activities. There are several more presented in my written testimony.

I would like to add that autism research is a major priority for the NIH, and we are committed to continuing to work to expand our efforts.

I have tried to stick as closely as I could to the 5-minute limit, Mr. Chairman, so that concludes my prepared statement, but I would be pleased to respond to any questions you might have.

Mr. BURTON. And your full statement will appear in the record. Dr. Cook.

[The prepared statement of Dr. Hirtz follows:]

TESTIMONY OF

DEBORAH G. HIRTZ, M.D.

NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE
NATIONAL INSTITUTES OF HEALTH

BEFORE THE COMMITTEE ON GOVERNMENT REFORM
U.S. HOUSE OF REPRESENTATIVES

OVERSIGHT HEARING ENTITLED
"THE CHALLENGES OF AUTISM – WHY THE INCREASED RATES?"

APRIL 6, 2000

Mr. Chairman, I am Dr. Deborah Hirtz of the National Institute of Neurological Disorders and Stroke (NINDS) at the National Institutes of Health (NIH). I have been asked to appear before you today to give the Committee and the families of individuals with autism a sense of the NIH's ongoing and planned research and other activities related to autism. As a representative of the NIH, and more directly, of the member institutes of the NIH Autism Coordinating Committee, I want to explain that we share the sense of urgency that individuals with autism and their families and advocates feel with regard to unlocking the mysteries of this devastating disorder. I will try to convey to you the strong commitment of the NIH to increasing our knowledge about autism - what causes it, how best to diagnose and treat it, and we hope not too far in the future, perhaps even how to prevent this dread disorder.

CHARACTERISTICS OF AUTISM

Autism is a complex, life-long, developmental disability that results in difficulty with social interactions, problems in communication, and restrictive or repetitive interests and behaviors. There is considerable variability in the severity of the symptoms, and intellectual function can range from profound mental retardation to above average performance on IQ tests. Epilepsy also occurs in about 30 percent of individuals with autism. Approximately 20 percent of children with autism reportedly experience a "regression;" that is, they have apparently normal early development, but then lose their ability to communicate and lose their social skills, usually sometime in the second year of life. Boys are three-to-four times more likely to be affected by autism than girls. Autism occurs in all racial, ethnic, and social groups.

NIH AUTISM COORDINATING COMMITTEE

I would like to briefly discuss the role of the NIH Autism Coordinating Committee (NIH/ACC). The NIH/ACC was established in response to a 1996 Congressional request that NIH establish a mechanism to coordinate its autism research activities and assure the most effective use of its resources. Its members include the Directors of the National Institute of Child Health and Human Development (NICHD), the National Institute of Mental Health (NIMH), the National Institute on Deafness and Other Communication Disorders (NIDCD), and the NINDS, as well as the program staff who manage the autism research portfolios of these institutes. The committee was recently expanded to include advisory representatives from the National Institute of Environmental Health Sciences (NIEHS), National Institute of Allergy and Infectious Diseases (NIAID), and the National Center for Complementary and Alternative Medicine (NCCAM). Representatives from the Food and Drug Administration, the Centers for Disease Control and Prevention (CDC), and the U.S. Department of Education have also been invited to participate in specific topic-focused meetings of the NIH/ACC. The full committee meets at least three times a year to coincide with meetings of the Institutes' national advisory councils, and meets annually with representatives of autism research advocacy organizations.

NIH AUTISM RESEARCH

NIH supports research on brain anatomy and development, language impairment, co-morbid conditions such as epilepsy, mechanisms of attention, and behavioral interventions in autism, as well as research on possible genetic causes and mechanisms. Over the last five years, the total NIH funding for autism research has nearly quadrupled—from $10.5 million in Fiscal Year 1995 to $40 million in Fiscal Year 1999. In FY 2000, it is estimated that NIH autism funding will increase to $45.5 million.

INCIDENCE AND PREVALENCE

Unfortunately, we do not have a definitive answer to the question of what the true incidence of autism is. Estimates vary widely, but recent studies suggest that as many as one in 500 persons may be affected by some form of autism. Recent reports suggest that the incidence of autism may be substantially increasing. It is not clear that the reported increases can be accounted for by improved or expanded diagnosis, or by the increasing availability of educational and other support services, although these are surely factors. Appropriate large-scale studies, though time-intensive and expensive, must be done in order to develop definitive estimates of incidence. NIH recognizes the pressing need to do the work that will give us essential knowledge of the true prevalence of autism and the trends of that prevalence over time, and is actively working with the CDC to design studies that could yield this knowledge.

SCREENING AND DIAGNOSIS

Accurate and consistent early diagnosis of autism is difficult. To address this problem and in response to the requests of concerned parents, the NIH ACC institutes, working with the American Academy of Neurology, sponsored a 1998 conference on the State of the Science in Autism: Screening and Diagnosis. The conference included representatives of 12 major medical and other professional academies and societies, six parent advocacy groups, and representatives of the CDC and U.S. Department of Education. Attendees reviewed the existing research evidence for autism screening and diagnosis criteria. Current evidence suggests that symptoms of autism are measurable by 18 months of age, and autism can be reliably diagnosed by or before age three. Parents and expert clinicians can often detect symptoms during infancy, although a formal diagnosis is generally not made until the child fails to develop functional language by age two or later. Research is seeking to determine whether studies of home video observations of subtle motor and social behaviors may lead to behavioral diagnosis in the first year.

This research review became the evidence base for a subsequent meeting in January 1999, sponsored by the Child Neurology Society and the American Academy of Neurology. Based on the assembled research evidence, a consensus statement is being developed as a practice parameter, which is a professional guideline for recommended procedures, criteria, and timing for screening and diagnosis in autism. This will be the first time that such a multidisciplinary group has reached consensus on screening and diagnostic procedures in autism. A summary of the literature review was published in a special issue on diagnosis in the *Journal of Autism and Developmental Disorders (JADD)*, Vol. 29, (6), 1999, pp. 439-484). The specific practice parameter or clinical recommendations, once approved by the Boards of the professional societies, will be published in *Neurology*, and the *Journal of Child and Adolescent Psychiatry*, and are also expected to be published in each of the other professional journals representing medical or professional specialties that participated in the meetings. In endorsing these clinical guidelines, each of the participating organizations officially adopts these recommendations as the standard for autism screening and diagnosis.

CAUSES

Autism is not a disease, but rather a disorder in which there may be a number of different causal pathways. In the vast majority of cases, no specific underlying cause of autism can be identified. A variety of genetic, metabolic, infectious, and environmental factors may be important. A working group convened by NIH in 1995 reached a consensus that, for at least a significant subgroup of persons with autism, there appears to be a genetic susceptibility that most likely involves multiple genes, and NIH has conducted two major meetings on the genetics of autism. To date, genetic causes for Fragile X, the most common genetically inherited form of mental retardation that in some children produces many of the same behaviors and symptoms as autism, and the gene for Rett Syndrome, an autism-spectrum disorder, have been identified. In addition, genetic "hotspots," that is, potential chromosomal locations, for more classic forms of autism have been identified. NINDS, NICHD and NIMH are supporting a major pediatric brain imaging initiative to learn how the brain develops in normal infants, children, and adolescents which will provide potential control data for studies of developmental disorders such as autism. A data sharing plan will be implemented to make this resource available to the medical and research communities. However, much remains to be done. This includes more research into molecular genetics, normal immune system development, and the "regression" that occurs in some cases of autism. The NICHD- and NIDCD-funded network of Collaborative Programs of Excellence in Autism, in collaboration with CDC, is planning to launch a study of persons diagnosed with autism who regressed after apparently normal development, as well as matched comparison groups, which should yield valuable insights into potential risk factors and causes of autism.

TREATMENT

Although there is currently no known cure, nor treatment which can reverse all the symptoms of autism, interventions designed to alleviate specific symptoms are available. The best-studied therapies include educational, behavioral, and pharmacological interventions, and many children who receive intensive, individualized, behavioral interventions show progress in social and language skills.

In November 1999, NIH held a workshop in conjunction with the Department of Education on "Treatments for People with Autism and Other Pervasive Developmental Disorders: Research Perspectives" to evaluate the current biological, behavioral, psychopharmacological, and biomedical treatments in autism, and to identify critical research needs in autism treatment. The written reports and recommendations from the working groups at this meeting have only recently been assembled, and are currently being reviewed by the members of the NIH/ACC and representatives of autism advocacy groups to consider the next steps for incorporating these into the NIH autism research agenda.

Six rapid-turnaround, multi-site, double blind, placebo-controlled studies of secretin have been supported through the NICHD- and NIDCD-funded Collaborative Programs of Excellence in Autism. The results of one study have already been published in the *New England Journal of Medicine*, and the others are expected to be completed and published in the near future. In addition, NIMH-supported Research Units in Pediatric Psychopharmacology are conducting studies of risperidone, a drug which is used to treat autism.

CONCLUSION

The NIH/ACC institutes have conducted or supported a number of other activities related to autism research:

- Issuing a joint Program Announcement to solicit and encourage grant applications for research designed to increase our knowledge of the diagnosis, epidemiology, causes, genetics, and treatment of autism and autism spectrum disorders;
- Developing an overall autism information dissemination plan by the NIH/ACC public information officers, with input from the national autism parent organizations, to reach broader parent and health professional audiences, particularly with regard to research validated procedures for autism early screening and diagnosis;
- Conducting a workshop entitled "Building Animal Models for Autism Through Translational Neuroscience Research;"
- Supporting the creation of the Autism Tissue Program and its outreach activities under the auspices of the National Alliance for Autism Research and the Autism Society of America, and supporting inclusion of autism materials by other NIH-funded brain and tissue Banks across the country;
- Initiating the planning of a pilot study for a large-scale, longitudinal, multi-agency, multi-institute, prospective, population-based study to establish or rule out causal links between a variety of environmental events and normal or abnormal development, including autism. If supported, this would be the largest prospective

study ever undertaken, and would take several years to design and pilot study, before the full-scale study could be undertaken.

I have very briefly described some of the NIH autism research activities. Autism research is a major priority for the NIH. We clearly recognize that much remains to be accomplished, and we are committed to continuing to work to expand our efforts.

Mr. Chairman, this concludes my prepared statement. I would be pleased to respond to questions you and the members of the Committee may have.

Dr. COOK. Thank you, Mr. Chairman, for the opportunity to testify on the topic of autism. I am, as some have before, speaking as someone wearing three hats—actually, first, as the brother of the late Kenneth Wade Cook, who had many of the problems of children and adults with autism; I am also speaking as a child and adolescent psychiatrist who cares for many patients with autism, and as a biomedical researcher trying to increase our knowledge of the causes of autism and, above all, to try to increase our ability to treat this devastating disorder.

It starts with me recalling being an 8-year-old boy with a 2-year-old brother who my family had just realized was not developing normally. I remember vividly the pain of my parents. I further recall that we went to a meeting where, to my recollection—I will not speak for my parents—we were told that it was known from theory about what was known of the brain at that point that "patterning," a way of moving the arms and legs, a special diet, re-breathing through a mask, and related methods still practiced today in various forms, would cure his problems.

I remember our family being skeptical from the beginning of that meeting. However, by the end of the meeting, we and the other families in the group were sold on this treatment because it was too painful to accept what we knew was happening.

If there is anything I have not forgotten, it is that hope is something essential in working with children with severe challenges—for the children, for the families, and for all of us.

I am very thankful to those who were interested enough that far back in children with developmental problems to have spent so much time with my brother and my family and to be with us. They knew that providing us the tools to work to teach my brother the basics of communication and motor skills was very helpful, and I suspect that many of them were practicing this method for the same reason we were—they simply had to try.

I could complain about the 5 a.m. mornings in which as a child, it was physically exhausting to perform the patterning, but I am sure it was good training for being a physician-scientist, or perhaps a Congressperson.

However, I am not pleased that there was not more time spent teaching me to play with my brother instead of trying to teach him to read just to show that their method was working, when it was not even close to being an appropriate next step.

Our family learned to accept and love my brother deeply. I would like to add that at this time, the preferred professional response was to tell you to put your child away at birth. And some of our increased awareness, I am afraid, actually positively, is that we do not simply ship the kids away. We felt sort of like we were going against advice to keep him in our home, which we did for 10 years.

I am very thankful that children today have more opportunities for education due to congressional legislation. Excellent community support and model community support in St. Louis was vital to my family during my brother's last year. Mostly, I miss him deeply, since his death remains as unexplained as his original problem, although the two are certainly related. It reminds me that not only is there much suffering, there is also death with this disorder.

465

Obviously, I am also a physician-scientist because I cannot accept this, even after he is gone. Having several hats, as brother, physician and scientist can be extremely painful. I recall my anger as a child when investigators found that patterning was not effective. As it turns out, I collaborate with people at the same institution at Yale today—but I wondered how could they do such a thing, and how could I now be in their shoes, now that I have studied secretin and have failed to find that it is working as much as initially claimed.

The only thing in my defense, frankly, fighting myself here, is to say that I actually shed a tear when the data were analyzed for secretin, because even though at the bottom of it, there is not a lot of plausibility, I do not care—I deeply wanted this to work. And that is probably what my anger is, that all these things have not provided what they say they will, and I am the first one who wants them to work.

So our laboratory, not being satisfied with the status quo, has worked on neurochemistry, neuroendocrinology, neuroimaging and neurogenetics of autism. The reason for our current focus on genetics is the data, not our impressions or our wishes, show it to be the most powerful influence on the etiology of autism—and many have been studied carefully—maybe not carefully enough.

It is not the only influence—I would agree with what has been said several times—it is certainly not the only influence in autism, and it is certainly not a simple, single-gene disorder. If it were, we would know for sure what that single gene was.

However—and this is very important—it is a rare event in my lifetime to realize that suddenly, molecular-genetic study of autism spectrum disorders provides one of the best scientific opportunities in medicine. I must say that usually throughout my career, I have had my passion, and my colleagues say, yes, it is very important, but there is no scientific opportunity; we cannot learn anything there. In genetics, we are actually ahead of most other medical disorders when we study autism.

In terms of why study genetics of autism, I think it is unlikely—and I would have said this before recent events—that gene therapy will be the result of genetic research in autism. It is also unlikely that genetics of autism will explain a relatively recent increase in measured autism prevalence.

The point of genetic research is to develop treatments that will correct the missing or abnormal signals for a small set of nerve cells in the amygdala, hippocampus and cerebellum so that the nerve cells mature. I very much agree with those who are optimistic on this point. These are not children who have brains that cannot further develop. That is my view, but it is a view as a scientist. You do not see the kinds of changes in the brain that would make things not able to move forward.

If we knew the signals, what has long been a too complicated puzzle of autism would become simple enough for us to understand. We are all challenged in a sense in trying to make sense of this. So although the simple idea is to provide gene therapy, oral delivery of more traditional small molecules, which we usually refer to as "medications," is likely to be more feasible and preferable, partly because there are few treatments that we have not wanted to take back. That is certainly something that I have learned as a physician—I try things, and they make sense, but if they do not work, it is time to stop them.

Two recent developments in the broader field of developmental disorders show that complex situation may be better understood through molecular genetics. The first is the finding of the gene for FRAXA, or Fragile XA mental retardation. This is very relevant to autism since a substantial proportion of children with FRAXA have autism spectrum disorders. Although one wishes knowledge of a gene will lead to new treatment sooner, the results of a decade of research in FRAXA to understand the mechanism of this disorder is leading to an almost exponential growth in understanding complex interactions of molecules in the process of learning.

Mentioned earlier, which is actually quite historic, was the recent finding of the gene for Rett syndrome, because this is actually finding a specific gene for an autism spectrum disorder. It is notable that it is caused by a single gene, MECP2, but that it has a course of regression in social behavior and communication between the first and second birthdays. Knowing the gene has led to a breakthrough in the systematic approach to investigation of Rett syndrome in terms of how it affects the development of the brain, and this is already moving us forward.

Although we do not know the specific genes involved—and I would agree with that, and it is definitely something that is personally frustrating today—several groups have been finding evidence that an extra part of chromosome 15 leads to a high risk for autism, especially if inherited from the mother. Believe me, based on the history of autism, if I could have it come out another way, I would; but this is simply the origin of the chromosome and has nothing to do with the mother's behavior, as the theory went in the past.

Although this is responsible for less than 4 percent of cases of autism, these 15q11-q13 duplications, like Rett syndrome and FRAXA, are helping us understand autism with regression, because all three of these often have this as a component, more generally.

Several laboratories including our own are searching for a gene in this region. As an example of our concern in genetics about not wanting to waste precious resources, the probability at this point of there not being a gene in this region is about 5 in 100,000 with the most rigorous blinded studies. But we are not sure yet, and that is just the way it has to be, because we may expend our resources in the wrong direction. We are close to sure at that level.

Of course, the problem is that we will have to get beyond regions with likely autism genes to actually finding the specific changes and then getting on with the work of using the information to improve treatment, because that is the point.

So it is a good thing there are people doing excellent clinical research and trying to improve educational and other interventions while we are working out the fundamental causes, with many others. However, it is important not to think we have more of an effect than we can back with controlled data.

The history of autism teaches that zeal without skepticism may have negative consequences. The first was blaming mothers, and the second was false accusation of fathers of children with autism of abuse when their children were undergoing facilitated communication. That was probably the biggest problem that we had last decade in terms of things that, on their face, should not have bad consequences but did.

The challenges of autism research are obvious. In terms of needs, I mostly want to thank Congress for the appropriation of increased funds for biomedical research generally. All of the pertinent NIH institutes are now actively engaged in the support of autism research.

A simple statement of needs is that there are many important and feasible questions about autism not able to be asked with current resources. There are not enough well-trained researchers in the field, partly because, in spite of the figures that they have increased, I question that it was much more than zero 5 years ago. Most importantly, questions that are being asked efficiently, such as in the area of molecular genetics and others, are not being answered at an optimal rate given current funding in this area. That is not OK for me, because my patients are aging with me, and more are being born. Again, I am not criticizing the funding but appointing a statement of scientific opportunity that we do not want to miss.

I thank you for the opportunity to communicate.

[The prepared statement of Dr. Cook, Jr., follows:]

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April 3, 2000

Honorable Dan Burton
Chairman
Committee on Government Reform
House of Representatives
Congress of the United States
2157 Rayburn House Office Building
Washington, DC 20515-6143

Dear Representative Burton and Colleagues:

Thank you for the opportunity to testify on the topic of autism. I am speaking as the brother of the late Kenneth Wade Cook who had many of the problems of children and adults with autism, as a physician who cares for many patients with autism, and as a researcher trying to increase our knowledge of the causes of autism and to increase our ability to treat this devastating disorder.

I recall being an 8 year-old boy with a 2 year-old brother that my family had just realized was not developing normally. I remember the pain of my parents vividly. I further recall that we went to a meeting where, to my recollection, we were told that "patterning," a special diet, rebreathing through a mask, and related methods still practiced today would cure his problems. I remember our family being skeptical for part of the meeting. By the end of the meeting, we and the other families in the group were sold on this treatment because it was too painful to accept what we knew was happening. If there is anything I have not forgotten, it is that hope is something essential in working with children with severe challenges. I am thankful to those who were interested enough in children to spend so much time with my brother and my family. They knew that providing us the tools to work to teach my brother the basics of communication and motor skills was helpful and I suspect that many of them were practicing this method for the same reason we were. They had to try.

I could complain about the 5 AM mornings in which it was physically exhausting to perform the patterning, but I'm sure it was at least good training for the schedule of a physician-scientist and provided a shared task for our family. However, I'm not pleased that there wasn't more time spent teaching me to play with my brother instead of trying to teach him to read, when it wasn't close to being an appropriate next step. Our family learned to accept and love my brother deeply. I am thankful that children today more opportunity for education due to Congressional legislation. Excellent community support was vital to my family during my brother's last years in St. Louis. Mostly I miss him since his death at the age of 29. His death remains as unexplained as his original problem, although the two are likely to be related. It reminds me that there is mortality as well as morbidity associated with autism and related developmental disorders.

We have an extremely long way to go to provide full access to adequate care for children, adolescents, and adults with autism. It is very difficult to confront attitudes as a physician that I only suspected as a child. Insurance companies, state agencies, school administrators, and other physicians continually turn away from caring for people with autism. Much more attention is given to paperwork than provision of care and services. This is not the main purpose of our meeting today, but I can not speak without mentioning this. Although many of the most severe problems are emotional and behavioral, insurance companies discriminate against the best treatments by the most qualified providers, with the result often being time lost from work for parents, depression in parents, and most importantly, suffering would otherwise be treatable.

The needs of the patients and problems in the systems of care and education have seemed overwhelming since I started my practice in the mid 1980s, so the thought of an increase in the prevalence of autism is probably something I wouldn't want to confront. However, comment on changes in systems that are largely responsible for the apparent increase is appropriate. An increase in autism in Illinois schools has been cited as evidence a rise in autism prevalence rates, but autism is still underestimated in Illinois schools. The increase is based on the introduction of autism as a possible educational classification in autism. In addition to many educational systems not recognizing autism, many diagnosticians didn't recognize it in the past. Autism spectrum disorders are only beginning to be accurately estimated. Based upon its widespread ethnic distribution, it has most likely been challenging people with autism and their families for thousands of years, but it has taken us this long to recognize what it is. Thus, the committee's ongoing work is important and a sense of urgency is necessary to catch up for lost time.

This brings to mind the medical saying, "first do no harm." One harm worse than doing nothing was blaming mothers because of their physical and emotional closeness to their children. Not only were individuals hurt by blaming mothers for their child's autism, but we probably lost a couple of decades following an impression of causation rather than focusing on the same science that was leading to improved treatments in cancer and heart disease. Without evidence to support a relationship between vaccinations and autism, we need to be careful about wasting precious resources on another case of guilt by association. Mothers were guilty because they were physically close to children with autism. Now vaccinations are being blamed largely because they are given at the same time as the regressions that occur for a substantial minority of children with autism (between the first and second birthday). Certainly, GI findings that have not been demonstrated to be specific for autism do not provide support for MMR vaccinations as a cause of autism. Data may be provided today which are credible in support of a connection, but the data to date do not support the hypothesis of MMR vaccination caused autism.

It has been a privilege to be involved in the development of new treatments for children with autism. Lost in the media's overfocusing on "miracle" cures over the more than three-and-a-half decades I have been involved, are small changes in our available treatments. Although limited to improving aggressive behavior, anxiety, and depression, medications that potently inhibit the reuptake of serotonin into nerve terminals (SSRIs)(e.g. Prozac, Luvox, Paxil, Zoloft, Celexa) have provided the first medication class that reduces the core symptoms of repetitive behavior leading to distress for many people with autism. Of course, it isn't enough, but it demonstrates that improvements through development of effective medications are possible. As far as research challenges and needs are concerned, pharmacological treatment research needs to be enhanced so that we have better data about whether each of these drugs works in autism, for which symptoms, at what ages, and for which patients. In addition, it would be extremely helpful to know which patients will worsen on small doses and what treatments to provide such patients.

As many know, not all of our attempts to improve treatment have been successful. A relatively classic story is that of fenfluramine, originally thought to raise I.Q. and reduce symptoms of autism. After considerable work, fenfluramine was found to be a good placebo. Although we were hopeful that secretin would be serendipitous powerful treatment, at least two carefully controlled trials have shown it to be similar in effect to fenfluramine in providing a good placebo effect. Further studies are ongoing to make sure a positive effect is not present under certain circumstances, but it may be about to end up as part of the long history of good, honest attempts to hit a home run in autism treatment that struck out. There is no reason not to try, except that we have to be careful about the risks to the children and the costs to the families if we overly promote treatments without evidence from controlled trials.

There is a problem when thousands of doses of secretin from pigs could be administered to children with claims of benefit while clinical trials to study safety and efficacy were being delayed by federal policies against expediting research review for secretin clinical trials. This ironic situation allowed the supply of secretin to be depleted, thus delaying initiation and completion of our multi-site trial.

Having several hats as brother, physician and scientist can be very painful. I recall my anger as a child when investigators found that patterning wasn't effective. How could they do such a thing and how could I now be in their shoes in contributing to data about the lack of efficacy of secretin? All I have to say is that I shed a tear when the data were analyzed for secretin, much as I shed many tears when I came to the realization that "patterning" was not going to let me know my brother without his severe problems.

I suppose it is obvious why so much of my time is devoted to research reaching down to basic mechanisms. On the one hand, I am desperate to improve the situation for my patients, many of whom are reminders of my brother. On the other hand, for some of my patients I have seen medical treatments provide relief I didn't think possible before our first use of Prozac in autism shortly after its release in 1988. By the way, there is no reason to have lengthy discussions about who tried it first, since I know I had parents discuss it around the same time or before professionals were considering it.

The riskiest thing for a physician-scientist to do is translational research, especially when it is from the bedside to the bench. Basic science has a much more appealing longitudinal logic. Clinical science has relevance. As much as both are pioneering, translational research often requires almost autistic perseverance. However, eventually the bridge has to be crossed.

Our laboratory has worked on neurochemisty, neuroimmunology, neuroendocrinology, neuroimaging, and neurogenetics of autism. The reason for our current focus on genetics is that the data, not impressions, show it to be the most powerful influence in the etiology of autism. It is not the only influence and it is not a simple, single gene disorder. However, it is a rare event in my lifetime to realize that suddenly that molecular genetic study of autism spectrum disorders provides one of the best scientific opportunities in medicine. Of course, this would not be possible without the considerable basic science advances and applied science advances ranging from sequencing of the human genome, to development of rapid methods of genotyping, to the development of powerful statistical approaches. It is new for established researchers in other fields to be drawn into autism and related disorders because of the scientific opportunity.

It is unlikely that gene therapy will be the result of genetic research in autism. It is also unlikely that genetics of autism will explain a relatively recent increase in measured autism prevalence. The point of genetic research is to develop treatments that will correct the missing or abnormal signals for a small set of nerve cells in the amygdala, hippocampus, and cerebellum so that the nerve cells mature. If we knew the signals, what has long been a too complicated puzzle of autism will become simple enough for us to understand. Although the simple idea is to provide gene therapy, oral delivery of more traditional small molecules is likely to be more feasible and preferable.

Even more important has been the emerging voice of families of children with autism. I can not begin to list and thank the parents, brothers, sisters, aunts, uncles, and grandparents who are not only taking on the extraordinary challenge of caring for their family members, but who are speaking for people with autism who because of their communication problems are not as able to speak for themselves as we wish they could.

The need to learn more about autism is self-apparent and the scientific opportunities are abundant. The challenges are in learning about something as complicated as the developing brain and development of some of the most uniquely human qualities of higher level communication and social behavior.

Two recent developments in the broader field of developmental disorders show that complex situations may be better understood through molecular genetics. The first is the finding of the gene for FRAXA mental retardation. This is very relevant to autism since a substantial proportion of children with FRAXA have autism spectrum disorders. Although one wishes knowledge of a gene will lead to new treatment sooner, the results of a decade of research to understand the mechanism of this disorder is leading to an almost exponential growth in understanding of complex interactions of molecules in the process of learning. Another development is the recent cloning of the gene for Rett syndrome. This is actually one of the most severe autism spectrum disorders. It is notable that it is caused by a single gene, *MECP2*, but that it has a course of regression in social behavior and communication between the first and second birthday. Knowing the gene has led to a breakthrough in the systematic approach to investigation of Rett syndrome in terms of how it affects the development of the brain. Study of both FRAXA and Rett syndrome will lead to basic knowledge about how autism and related conditions develop.

A72

Although we don't know the specific genes involved, several groups have been finding evidence that an extra part of chromosome 15 leads to a high risk for autism, especially if inherited from the mother. Although responsible for less than 4% of cases of autism, these 15q11-q13 duplications, like Rett syndrome and FRAXA, are likely to help us understand autism more generally. Several laboratories, including our own, are searching for a gene in this region. As an example of our concern about not wanting to waste precious resources, the probability of there not being a gene in this region is about 5 in 100,000, but we're not sure yet. Of course, we'll have to get beyond regions with likely autism genes to actually finding the specific genetic changes and then getting on with the work of using the information to improve treatment. (More information about molecular genetic studies and autism is available at our web site at: http://psychiatry.uchicago.edu/ldn).

It's a good thing there are people doing good clinical research and trying to improve educational and other interventions while we are working out the fundamental causes. It's also good that people are asking questions about prevention and even taking shots to improve medication delivery, either trying to hit for average with medications like Prozac, or swinging for the fences with an occasional secretin trial. However, it's important not to think we have more of an effect than we can back with controlled data. History teaches us that zeal without skepticism may have negative consequences (e.g. false accusation of fathers of children with autism who underwent facilitated communication).

The challenges of autism research are obvious. In terms of needs, I mostly want to thank Congress for the appropriation of increased funds for biomedical research. All of the pertinent NIH institutes are now engaged in active support of autism research. A simple statement of needs is that there are many important and feasible questions about autism not able to be asked with current resources. There are not enough well-trained researchers in the field, partly because the area was almost totally unfunded five short years ago. Most importantly, questions that are being asked well and efficiently, such as in the area of molecular genetics, are not being answered at an optimal rate given current funding in the area. Again, this is not meant as a criticism, but as a statement of scientific opportunity.

Thank you for the opportunity to communicate.

Sincerely,

Edwin H. Cook, Jr., M.D.
Associate Professor of Psychiatry and Pediatrics

Mr. BURTON. Thank you, Dr. Cook.

Let me start the question with you. Do you subscribe to the theory that part of the problems of kids getting autism is caused by the vaccine?

Dr. COOK. I guess that is a direct question to me, having evaded that.

Mr. BURTON. Yes.

Dr. COOK. I have heard more today than I knew before I came. I did not specifically address that because I have not directly studied the question.

As I see the data at this point, the data do not support the idea that vaccines cause autism. As someone who studied secretin as an example, I realize that I cannot prove the absence of something. For example, on secretin, all I can say is that I have proved the absence of it for myself; if someone else wants to come and only treat a certain kind of child in a certain kind of setting, then perhaps our work will have helped them.

Mr. BURTON. What would you think, Doctor, of taking a hard look at the conclusions that Dr. Wakefield and Professor O'Leary and Dr. Singh came to with their research? I know you work on genetics, but what would you think about looking at their research?

Dr. COOK. Well, in some ways, I work in the area of clinical trials, so I can comment on why they fail to convince me that there is a connection. They have raised the possibility of a connection, but there are several areas in their logic that do not come together. It may be that if they were up here, they would say, yes, those are gaps that we have to fill—but I am concerned that in the presentations, starting with the original paper and today, they have not sufficiently highlighted where the gaps are, so the logic falls apart in a few places.

First of all, if we know that we have prevented a lot of autism by preventing rubella-caused autism, which was a prevalent cause 20 or 30 years ago, as Dr. Chess showed, then why is it now MMR, and all of a sudden, it is measles?

Now, if someone is so pleased—and I must say it is fairly fancy methodology in terms of pulling the measles virus out—why not show that they can pull the measles virus out from the vaccine, differentiated genetically from the measles virus that would occur without the vaccine?

These are holes, and my main thing is what I hear from the positive side is an almost total lack of self-criticism, OK? That is a key point——

Mr. BURTON. But——

Dr. COOK [continuing]. That is a key point of the scientific method.

Mr. BURTON. But you do not think that their research is worth taking a look at?

Dr. COOK. Oh, I think their research is very interesting, and I think it is particularly interesting to what I think—and this is an interesting epidemiological question—if there is autistic enterocolitis—and I think they have interesting data—how much of the total group of autism is it? From what I have seen, it would not be nearly enough of autism to account for an increase in prevalence.

Mr. BURTON. You heard the—and I am going to go down the line with the rest of you in just a minute——

Dr. COOK. If I have a child who is vomiting, I very much agree with the——

Mr. BURTON [continuing]. You heard the testimony of the four parents as well as the testimony I gave about our grandson; and within just a day of their getting these shots, their temperatures went up, and they started the violent reactions, and it got worse. How would you account for that? Is that just a coincidence, or what?

Dr. COOK. Well, if I am to take that as a reason for their autism to be caused, then I will agree with the parents who told me their child had autism because they took a 2-day trip, leaving the child with very good grandparents; they came back, and the child had autism suddenly. Am I supposed to now tell them, yes, you are right, because you see the connection—because of a potential coincidence—you are right and caused it by taking 2 days off and leaving your child in very loving hands?

I think we have got to be very careful and use careful epidemiological approaches. Dr. Taylor has done the best epidemiological study. There is not another one on the other side. If there were, I would weight it—in fact, I would give more weight to a positive, well-done epidemiological study. We have only got one.

Mr. BURTON. Well, I am not a doctor, but it just seems to me that the scientific community ought to have their minds open to all possibilities as far as the causes of autism are concerned. From your testimony, you sounded like it is a gene problem, and the vaccines could not possibly be a contributing factor.

Dr. COOK. No. They could, but the people who think they could, the people who want to raise the hypothesis—and I am someone who has spent a lot of effort testing other people's hypotheses—I think there is a lot of duty when people raise a hypothesis, including Dr. Wakefield, from GI studies, who raise an epidemiological hypothesis, I think it is his responsibility to test the hypothesis carefully. I have thrown out hypotheses that I quite loved, and they were great—they were not all genetic; some were immunological—but you have to go with the data. If I have the data, I will go with it.

Mr. BURTON. When you studied secretin, did you study more than one dose?

Dr. COOK. No. As a matter of fact, before we did the study, there was a meeting which included people who were convinced that secretin worked who said it was one dose, and we used the dose it was supposed to be; we used porcine-derived secretin—and now, all of a sudden, the hypothesis shifts. Now, the hypothesis shifted to multiple doses—that is fine. The people who think it is multiple doses and single doses now have to test it. And if we have helped to refine the hypothesis so they can do a better study and show that it works, then I am fine with that.

I recognize that basically, science cannot disprove anything. It is really meant to—you have to actually set up a hypothesis to tear apart to accept the other one. That is what I mean by part of the self-criticism of the scientific method.

So absolutely—if this gets turned around in particularly children with projectile vomiting—that is a very rare group of autism—but somebody with projectile vomiting, maybe 30 kids like that, secretin would work wonderfully.

Mr. BURTON. Dr. Hirtz, we were talking about the study at Brick Township, NJ. I do not know if you heard me ask the question of the doctor from the CDC earlier. Why would you think that the National Institutes of Health and CDC and others would go into Brick Township, NJ and look at all the environmental problems that may have caused the autism epidemic they have had there, and when the parents asked that they check to see if any of the vaccines had anything to do with it, why would you think the health agencies did not check that as well?

Dr. HIRTZ. I am sorry, Mr. Chairman, I am not at all familiar with the study at Brick Township; that was conducted by the CDC, not the NIH, and I am afraid you will have to ask them questions about it.

I would be glad to tell you about activities that the NIH is doing in this area, however, if you would like to hear some of them.

Mr. BURTON. What would you say about the NIH taking a hard look at the studies done by Dr. Wakefield, Dr. O'Leary, and Dr. Singh, and some of the theses that Dr. Megson espoused earlier?

Dr. HIRTZ. I think that examining scientific evidence is always a useful thing to do; there is nothing wrong with that. In terms of the vaccine issue, I would just like to say that you are right—we do need to keep our minds open. I do feel that at this time, the available, valid scientific evidence does not support that vaccine is a cause of autism.

However——

Mr. BURTON. What bothers me about a lot of this is Dr. Cook and you say if there is a hypothesis that says this, it has to be proven before we will even take a hard look at it.

Dr. HIRTZ. No——

Mr. BURTON. Well, that is the impression that I am getting, and——

Dr. HIRTZ. May I finish?

Mr. BURTON [continuing]. Let me just finish. The problem is that there are a large number of children who have acquired this problem shortly after getting these vaccines, and when scientists and doctors from other parts of the world come up with a thesis, I think it is irresponsible to out-of-hand just discard that and say, well, that is something they have to further prove, because their hypothesis has not yet been proven. It seems to me that you say, hey, if there is a positive result there, if it looks like there may be something there, why don't we take a look at it, too, instead of keeping yourselves confined to one area?

Dr. HIRTZ. If you will let me finish, Mr. Chairman, I was going to tell you about all the efforts we are making to look at that. What I was going to say when I continued was that even though that is the case at the moment, we do take this very seriously, we take the concerns of the parents very seriously, and when we have reports like this and concerns like this, we do address them.

We are taking three steps at the NIH, and we are undertaking three projects to look at the relationship of vaccines and autism.

One of them is very immediate and is going to be done in the centers that now exist. The Child Health Network has Centers of Excellence in autism, and they have about 1,000 children enrolled. In conjunction with the Deafness and Communicative Disorders Institute and the CDC, they are going to look at the children who have regressed and look at their vaccine histories and study this issue, compare them to other children. That is going to be done as soon as possible, hopefully, this fiscal year.

In addition to that study, something I have been working on, we are planning at the NIH to look at the very important issue of not only vaccines but risk factors for development of autism as well——

Mr. BURTON. I have had a number of people today testify from the health agencies that there is no scientific evidence that autism is related to vaccines. How do they know that?

Dr. HIRTZ. They do not.

Mr. BURTON. How do you know that? A vaccine is put out on the market, children all take it——

Dr. HIRTZ. On the——

Mr. BURTON [continuing]. Let me just finish—and there is an increase from 1 in 10,000 to 1 in 400 or 500, so we have an epidemic on our hands; and yet the health agencies of this country are telling us there is no connection between these vaccinations and autism. How do you know?

Dr. HIRTZ. I do not know that there is no connection. What I know is that the evidence that has been reviewed by the British Medical Research Council and the epidemiologic evidence does not support a large-scale causation. But I still think——

Mr. BURTON. How do you know that?

Dr. HIRTZ [continuing]. But I still think that there are and there may be certain children who are susceptible, and that is what we have to go after. It is very important that we look for why children develop autism and whether there might be a small minority of children who have some susceptibility, and we are not ruling that out.

Mr. BURTON. Yes. One of the things that concerns me—and pharmaceutical companies are extremely important; they employ an awful lot of people in my district and in Indiana; we have some great pharmaceutical companies that have saved a lot of lives and probably kept epidemics from happening around the world, there is no question about that—but there are so many people who work at CDC, HHS, NIH, and the other health agencies who have some kind of connection to the pharmaceutical companies and are on these advisory boards, that it causes one to wonder whether there is thorough research going into these things before they are approved.

Does that concern you at all?

Dr. HIRTZ. At the NIH, we do not really deal with the approval process of the vaccines. Other agencies can tell you more about how they deal with that.

What I am really concerned about—it is hard for me to convey to you that we really—there is nothing I would not do to stop autism from occurring and to stop children from developing this order, but I——

Mr. BURTON. Well, then, what I would suggest is that we are going to get all of these studies—I am going to get them—and we are going to send them to all the health agencies, and I want the health agencies to write back and tell me, after they do some research, whether or not they feel there is any merit to these arguments. And I want them to look at—and I will get other Members of Congress to join me if necessary—I want them to look at Dr. Wakefield, Dr. O'Leary, Dr. Singh, Dr. Megson—all of the doctors who have come here today with various solutions that have worked—Dr. Upledger with his cranial manipulation. Those things should all be looked at, because we are giving the health agencies in this country billions and billions and billions of dollars, and for them not to look at every avenue for possible treatment for these things I think would be wrong.

Let me just go down to the end of the table and give all of you a question—Drs. Rimland, Goldberg, Megson, Upledger, and Ms. Pratt.

Do you think from what you have heard today and seen in your scientific research that there is a possibility that the vaccines are contributing to the increase in autism?

Mr. RIMLAND. There is not only a possibility, there is an extremely high likelihood.

Mr. BURTON. Would you pull the mic closer?

Mr. RIMLAND. There is not only the possibility, there is an extremely high likelihood from all the evidence available, including the so-called anecdotal evidence that people like to snicker at, but which is really very important evidence, from the kind of evidence that Dr. Wakefield submitted, from the rise in autism at the time of initiation of the MMR, the time of the rise of the epidemic, the data that I provided in my handout which shows that late-onset autism started at just about the same time that the MMR was initiated. There is just a world of evidence that leads me to think that it is extremely likely that when the final answer is known, if it is ever known, the MMR will be strongly implicated as an important cause of autism.

Mr. BURTON. Dr. Goldberg.

Dr. GOLDBERG. With caution as I say this, as a practicing pediatrician, I have vaccinated children in my practice whom I considered high-risk—I have literally had a godchild with one foot in autism and one foot out and vaccinated her along the way. As I stated this morning, I however try to practice vaccination policies that I was taught 20, 30 years ago—you do not vaccinate an ill child; you use certain plans; I never gave a child a hepatitis B shot in the nursery yet. But I think that the effort to solve autism gets distracted by the fact that we do have a lot of children triggered off by some time correlation to the vaccine.

As I mentioned in my testimony, I think that if we are going to understand this, we need to step back and figure out why there is a wealth of science that says, hey, the vaccines do not create this or cause it, and then we suddenly have this epidemic going on, and I really believe the way it will come out in the end, whether we do it in the next 6 or 8 months or in 10 years, is going to be that this will all tie in from the eighties and nineties with what is going on in our population and it is not specifically the vaccines, but the vaccines are playing a role in it.

Mr. BURTON. Would play a role in it.

Dr. GOLDBERG. Pardon?

Mr. BURTON. The vaccine would play a role.

Dr. GOLDBERG. Yes, the vaccines would play a role. But we need to understand why, suddenly, a population has become susceptible to those when they did so much good along the way.

Mr. BURTON. Dr. Megson.

Dr. MEGSON. I am seeing more and more families that are completely devastated. I know one mother who has been very active in the parent support group in our local community has had three children. The oldest has severe dyslexia/ADD; the second one died of SIDS within 24 hours of DPT; and the third one is autistic.

If my theories are correct, there is an organ in the neck at the base of the main artery to the brain called the carotid body, and we are disconnecting the pathway. When the oxygen-level in the blood decreases in the carotid body, there is a signal sent to the respiratory center in the brainstem to increase breathing rates, and we are disconnecting that pathway.

Recently they discovered that, oh, if you put children down to sleep on their backs, they do not die of SIDS. I think we really need to look at this.

I do not want to be here. I have never gone against the grain. I am not a vaccine researcher. But once I discovered some of these connections, I do not think any of us can turn our backs. So many families are devastated.

Mr. BURTON. Thank you.

Dr. Upledger.

Dr. UPLEDGER. I have to say yes, I do. As I stated earlier, I think there is a group of autistic children—and by no means do I say all autistic children—whose problems are due to membrane dysfunction. But I have learned to understand that a significant number of them do, and I can easily differentiate autism from childhood schizophrenia just based on the feel of the membranes.

I think that the membrane is a place where several factors may go, and it can be, as I said, a fever due to a virus, it can be a vaccine reaction, it can be a traumatic delivery—it can be anything that creates a change in the membrane flexibility and growth accommodation.

From the histories I have taken—and I have taken histories with autistic parents since 1975—it is more than coincidence as far as I am concerned. I do not know how many cases of anecdotes we need to consider that the anecdote has some validity, but it would appear to be that it is infinite. We still will not believe the anecdote. I happen to subscribe to the idea that if you study the anecdote, you might learn something.

So I would go very strongly in favor of the idea that vaccines are potentially able to cause autism in terms of their effect on membranes. I think that membrane condition is probably largely influenced by genetic factors along with nutritional factors, along with toxic factors, and so on, so you have a susceptible membrane.

I have opened up enough human heads that are not embalmed, that are maybe 4 or 5 hours old, and I can see the difference in

479.

the membranes, and when you look at the diagnoses, you begin to put 2 and 2 together.

I think one of the major things that has happened in medicine is the meningeal membrane system has been given a very short shrift. It is a very important system. It has just come out recently—I cannot think of his name now, but a fellow from California, UC San Diego, I think, came out with evidence, very strong evidence, that 1 gram of dura mater membrane, which is a very small quantity of that membrane, carries 100 million single-domain magnetic crystals that are ferric.

What does it take to change that? The brain itself has 5 million per gram. Anything that interferes with electrical conduction or magnetic fields is going to screw up that brain function. When we stretch that base membrane laterally, why does the kid get better in terms of his emotion? Because I think we are improving the conditions under which his temporal lobes have to live. That is why. You can tear it all apart, and if you study temporal lobes, you can say, OK, temporal lobes cause autism. But what caused the temporal lobe, and what caused the membrane to not accommodate the temporal lobe? When you start looking at it that way, you start looking at multiple factors any one of which can be causal—and I put vaccine in that category.

Mr. BURTON. Thank you, Doctor.

Dr. Pratt, do you have a comment?

Ms. PRATT. I think it is a very hard issue, and from both the autism side of America and the Indiana Resource Center for Autism, our job is really to provide information for families. And it is very hard when you listen to very well-respected scientists and researchers like Dr. Cook, whom I have tremendous respect for—and I point him out because he is in Illinois, the State neighboring Indiana—it is very hard when you hear the testimony and the research that says there does not seem to be a link, and then, when you hear from the families their stories. Balancing that out is a very difficult thing, and I struggle with that, because I do not want all of us running down one path, hoping that, yes, at the end of that path is going to be a cure or the reason or whatever.

I hope we can all keep our minds open to all possibilities. Again, to be an ethical and decent professional, I have to say to families that I am hearing some stories, and there is a possibility for it. Those families and the families that you have heard from today really cannot wait for the research to tell them conclusively that there is a relationship.

I would say that in all likelihood, Congressman Burton, if your daughter had another child, she would take a very serious look at the usage of vaccinations with her third child, regardless of what the research tells her. That is the complexity of the issue.

So, what you have heard over the last several hours today is a lot of different testimony and sometimes conflicting testimony, and I hope that what we will all focus on is trying to uncover the complex nature and perhaps the complex causes behind autism.

Mr. BURTON. Thank you.

Let me just ask Dr. Cook one more question, and then I want to make a couple of announcements before we conclude.

Dr. Cook, how do you account for these parents and these doctors finding the measles virus in the guts of these kids who have had the MMR shot?

Dr. COOK. I am very interested in that finding because I think it is a fascinating finding even if it applies to one in 1,000 kids with autism. Each child is very valuable. So first of all, realize that Dr. Wakefield is talking about a very small group of autism, with documented pathology, with vomiting—which, as I said, is quite rare in autism. I think that is an interesting finding that needs to be followed up.

The next step of that may not be a link with vaccines and autism; it may be something quite more important in understanding what is happening with autism. So that some of what was presented today, it was very good to see data ahead of time; it is rare, and it is nice of them to share it. There is something about their work, particularly seeing more controlled data than I have seen before, that is very interesting, and I will be paying quite a bit of attention to, because we need every clue that we can get.

Thank you.

Mr. BURTON. Very good; 1 second.

[Pause.]

Mr. BURTON. Let me just ask you a couple more questions, Dr. Cook. Where do you see the autism rates in the next 10 years? Do you see them pretty close to where they are now, or do you see them increasing?

Dr. COOK. I think if we are talking about from the perspective of school districts, they will continue to rise, because I think we are still underestimating across all school districts.

In terms of the actual prevalence, meaning all the children who have always been out there suffering from this, I do not see it going up that high. What I see is appropriately—and this is a very important, I think almost civil rights movement—these kids and families are being heard now. But I do not see this as an epidemic in the sense of prevalence. I see it as an epidemic in terms of a wake-up call that lots of kids and families have been suffering for a long time.

Mr. BURTON. So you are saying the 1 in 10,000——

Dr. COOK. It was never—I do not know——

Mr. BURTON [continuing]. It was always a lot higher than that?

Dr. COOK. I do not know of a 1 in 10,000. I know that 2 to 4 per 10,000 is what DSM3 said, which was 1980 to 1987. And 1987 has been referred to as around the time of an increase. That is when we went from DSM3 to DSM3R. The reason is DSM3 said the child had to have a pervasive lack of responsiveness. Now, I do not know who these kids were who had autism then, because every child with autism is related; they are just not related in the same ways. So now you have increased the definition as of 1987—and I think I have lost the question. I am sorry.

Mr. BURTON. It was about the projected increase in the next 10 years.

Dr. COOK. Right. So the most important thing about the 2 to 4 per 10,000 estimates is that they were often done by, well, let us say someone has come in to a university clinic, and you estimate that against the population. What has happened, which is better epidemiology since then, is you go knocking on every door.

So I have heard 1 in 500 referred to more than just autism, but the best study where they knocked on every door, half a million in Japan, found 1 in 500 for autism. So I do not think we are estimating it yet in terms of its impact.

Mr. BURTON. Do any of the rest of you have any projections or guesses on that?

Mr. RIMLAND. In California, the increase started in 1977 before the diagnostic changes were made, so the switch from DSM3 to DSM4 cannot even begin to account for that.

Dr. GOLDBERG. If I can tie in a projection, unfortunately, I can remember discussions back, literally, in the mid-eighties with clinicians, and at that time, the CDC, the NIH and everyone was saying this new entity out there that we were calling "chronic fatigue syndrome" or whatever it was supposed to be did not exist, or was not in any big numbers, and as clinicians, we were saying we were going to see 1 to 3 percent of the population. Well, now we are in the late nineties, the numbers are getting very close to that, and we are now talking 5 or 10 percent.

I think that if this is the same crossover to the children as was seen in adults, you can make a prediction that in the next 5 to 10 years, you may hit 5 or 10 percent of our population or more.

One of the most scary moments in my life recently, literally, was coming back on a flight from giving talks in Australia. I remember there was literally not a family who did not know a family who did not know a family that either had chronic fatigue syndrome, ADD, or autism. My thoughts on the flight coming back were, well, where is Australia—near the ozone hole—but my big concern was that that was going to be our country 5 or 10 years later. In the last month, I have literally had three families in—this is only a year and a half from that flight—telling me they do not know a family that does not know a family that does not know a family. This is a major crisis.

Mr. BURTON. Any other comments?

[No response.]

Mr. BURTON. Let me just end by thanking all of you. I really appreciate your being here. I have two grandchildren—one got a hepatitis B shot and stopped breathing within an hour; the other one got nine shots in 1 day and had a temperature of about 105 and became autistic, slamming his head against the wall, running around screaming. That is two for two. I guess maybe I am just one of those unfortunate statistics. But I have got to tell you, I think the problem is much greater than we believe, and I do believe, I personally do believe the vaccines have something to do with it.

Now, my position, since I am not a scientist, is really not one that most people are going to pay much attention to, or the parents who testified here today. But, what I do want to do is take all the scientific information that we have acquired today from you, from all the other doctors, and submit that to the health agencies of this country and ask them to do a thorough study of all of them to see if there is any validity to what we think the problem is. If they do that and do it thoroughly, and they report back to the Congress, it will be a real service to the American people.

Yes, Dr. Rimland.

Mr. RIMLAND. I think it is rather interesting that most of the official authorities are taking the position that the increase in autism is unrelated to the vaccine use.

One of my favorite expressions—I do not know who said it; I heard it one time, and I have tried to find out who said it, because I think it is extremely true—is "The chronicle of man's progress is the history of authority refuted."

Mr. BURTON. Well, thank you very much.

Thank you, ladies and gentlemen.

I have two very quick announcements. The NIH is having a meeting for parents of children with autism tomorrow morning from 10 a.m. to noon at the Natcher Auditorium on the NIH campus in Bethesda. If you would like to attend, you are welcome to attend that.

And we need to announce that the Unlocking Autism group is having a reception in HC–5 in the Capitol immediately after the hearing.

Thank you very much. I appreciate your being here. We stand adjourned.

[Whereupon, at 5:25 p.m., the committee was adjourned.]

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EFF-089 (5/2002)